VIRUSES FROM PRIMEVAL TIMES

TEXT: CATARINA PIETSCHMANN

No life is free of viruses. On Earth, at least, no organism seems to be spared from them. Susanne Erdmann and her team at the Max Planck Institute for Marine Microbiology in Bremen are studying viruses of the archaea, tiny single-celled organisms that lack a cell nucleus. Her research team investigates virus-like DNA elements, which may help us to explain how viruses actually originated.

As life on Earth emerged, the weather was bad, really awful. It rained – continuously – for 40,000 years and that was how the oceans formed. At the time, Earth was a rather unpleasant place in other ways as well. Meteorite impacts devastated the still young planet, and volcanoes ejected ash and sulfurous gases into the atmosphere. From the deep ocean floor, mineral-rich water at temperatures of up to 300 degrees Celsius bubbled up from hydrothermal vents.

Approximately four billion years ago, against all odds and adversities, the first cells formed: the "last universal common ancestor" (LUCA) of all bacteria, fungi, plants, animals – and archaea. Previously referred to as archaebacteria, these single-celled organisms have, to this day, retained many of their original characteristics: like bacteria, the cells possess no nucleus and no organelles. They are surrounded by a simple cell membrane of unique lipid molecules that are only found in the membranes of archaea protected by an outer layer composed of protein. In addition to the similarities they have with bacteria, archaea also share fundamental properties with nucleated cells.

Archaea, that are thought to be "ancient", also have to deal with pathogens likely from equally ancient times. "It's hard to believe, but even cells this small, on average just a thousandth of a millimeter in diameter, are infected by viruses," says Susanne Erdmann. While bacterial viruses have been studied intensively, very little is known about archaeal viruses. "More than 3,000 bacterial viral genomes have been sequenced, but not even 300 archaeal viruses. Of these, just under 100 viruses have actually been isolated, and all but one are from extreme environments." While the shape of bacterial viruses are already odd, reminding of space probes, the archaeal viruses are even more extraordinary in shape. Many of the archaeal virus particles, resembling for example spindles or bottles, are unique and unlike any bacterial viruses or viruses infecting nucleated cells.

Not always harmful to their hosts

Since 2019, Susanne Erdmann is a group leader at the Max Planck Institute for Marine Microbiology in Bremen, researching the special relationship

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PHOTO: TOM HEGEN

KNOWLEDGE FROM

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In southern France, seawater evaporates in artificial ponds to extract salt. Depending on the salinity, microorganisms color the water in different nuances. Such extremely saline lakes are also the habitat of archaea.

PHOTO: ACHIM MULTHAUPT FOR THE MPG

between archaea and their viruses. "Every virus I've ever isolated reveals a new surprise," says the biologist. What is particularly perplexing is that a great number of viruses do not seem to harm their hosts. They don't destroy the cells and only minimally affect their growth. The researchers are attempting to find out why. Viruses essentially consist of genetic material and a capsule of proteins. Many archaeal viruses also possess an envelope of lipid molecules. They are not cells and lack any metabolism of their own. They need a host cell to reproduce. As such, they are not considered to be living organisms. Erdmann and her team are hoping to find out more about the origins and evolution of viruses from the relationship between archaeal hosts and their parasites. Were today's viruses, which are frequently pathogenic, originally beneficial to their hosts? What was their original function, and how did they evolve into what they are today?

Some researchers suspect that viruses pre-date cellular life, which only later developed from those early viruses. However, this hypothesis assumes that the first viruses were able to replicate without cells. No evidence has been found for that so far. Another possibility is that the first viruses were small, parasitic cells that lived inside other cells. Over time, so the theory goes, these parasites lost some of their genes and came to rely increasingly on their host. Some

Left:
Archaea and their viruses are so small that Susanne Erdmann can only view them under an electron microscope.

Below:
This electron microscopy image shows pleolipoviruses at 50,000 times magnification. They infect cells of the archaea *Haloferax volcanii* without harming them. The viruses leave their host by budding off from the cell membrane. They are surrounded by a lipid membrane (light circles).

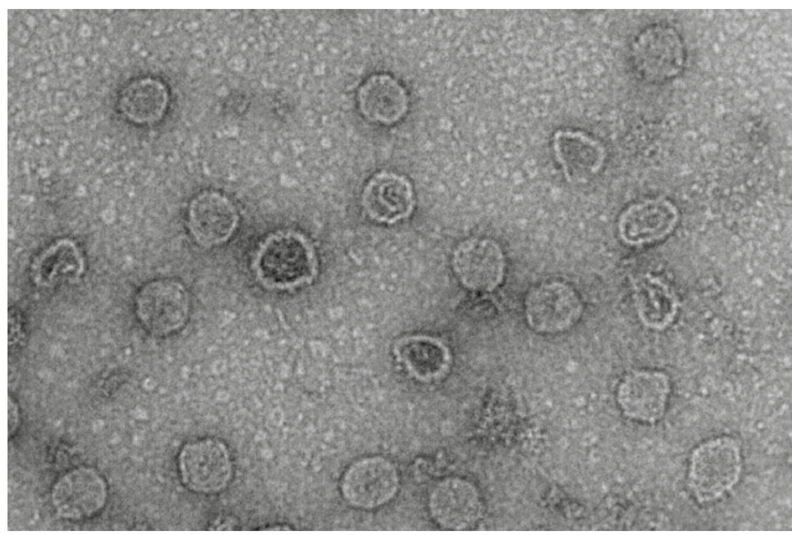

IMAGE: SUSANNE ERDMANN/MPI FOR MARINE MICROBIOLOGY

researchers suggest that the discovery of so-called “giant viruses” supports this hypothesis. In terms of their dimensions, some viruses of this kind are actually larger than bacteria and possess more than 1,000 genes (Sars-CoV-2 has only around 30 genes).

Max Planck scientist Matthias Fischer from Heidelberg is researching such giant viruses (see Max Planck Research 3/2019). However, he suspects they evolved not from cells but from smaller viruses that over time picked up more and more genes from their hosts. Another theory suggests that viruses initially arose from small fragments of cellular genetic material that excised and went on to replicate independently of the rest of the cellular genome. These fragments of genetic material could then have exited the cell in a vesicle formed from the cell membrane and entered other cells, collecting new genetic information over time. “The first ‘viruses’ probably passed from one cell to the next in membrane vesicles,” says Susanne Erdmann. Archaea love extreme habitats; they really flourish in hostile biotopes. *Pyrococcus furiosus*, for example, lives in and around geothermal vents on the ocean floor and can withstand temperatures of up to 113 degrees Celsius, thanks to its heat-insensitive proteins. For *Haloferax*, on the other hand, conditions can not be salty enough. These cells live in the extremely salty Dead

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Sea and can also make themselves at home in sea salt extraction plants. Others, for example *Sulfolobus alcidocaldarius*, would find even pure vinegar too bland. They grow best at a pH of 2.0 in acidic, sulfur-rich volcanic springs. However, archaea also live in very ordinary habitats – but, once again, they do so with distinctiveness. Some of them – the only living organisms to do so – are capable of generating methane. Methane is a greenhouse gas, which is produced when microbes break down biomass in the absence of oxygen. They inhabit oceans, swamps, rice fields, muddy soils, and even the digestive tracts of some herbivores.

An early love

Susanne Erdmann first heard about these 'strange microorganisms' while training to become a nurse. "I thought they were so cool – especially the ones living in extreme habitats." The microbes with their incredible diversity sparked her interest. That fascination steered her away from a career in a hospital to the University of Halle, where she studied biology. Her first direct contact with archaea was during an internship in Copenhagen. "I got to study the viruses of archaea from hot springs, which was really fun. They are much smaller than the archaea, and yet they are incredibly diverse and creative when it comes to controlling their hosts. But in order to study them, I had to spend four weeks sleeping in my car, because Copenhagen is expensive, and I couldn't find any affordable accommodation," says Erdmann. Subsequently, for her undergraduate research project she studied the proteins of a very unusual archaeal virus that is capable of changing its shape, and for her doctoral thesis she isolated several previously unknown viruses.

Susanne Erdmann was also particularly interested in the archaeal immune system, known as the CRISPR system. Difficult to pronounce, this antiviral defense has become very famous in recent years. Last fall, the Nobel Prize for Chemistry was awarded for the discovery of one of gene technology's sharpest tools – the CRISPR/Cas9 "gene scissors." The genome editing technique based on the CRISPR system allows researchers to modify DNA far more easily than in the past.

SUMMARY

Archaea are similar to bacteria, but represent a separate branch that splits off early from the rest of the ancestral tree of life. Archaea have retained some of their original characteristics to this day.

Like other forms of life, archaea are affected by viruses. However, these viruses frequently do no harm to their hosts.

In archaea, researchers have discovered a potential transitional form between a mobile DNA element and a virus. The discovery supports the hypothesis that viruses originated as segments of the cellular genome that were able to surround themselves with an envelope and bud off the cell.

CRISPR is an adaptive immune system that enables archaea and bacteria to specifically adapt to a particular type of virus. However, the CRISPR system does not get activated against some of the viruses that Susanne Erdmann has studied in the lab – just why not is still unclear. Instead, some of these viruses seem to live in a kind of symbiosis with the archaea: they reside permanently in the cells, multiplying and producing viral particles. The host cell remains intact and receives new genetic information in exchange.

After her residence in Copenhagen, Susanne Erdmann moved to the University of New South Wales in Sydney. She became interested in the habitat being studied there: the Deep Lake in Antarctica. Its water is saturated with salts, so it does not freeze, even in extremely cold weather. The lake is almost 40 meters deep and the water temperature at the bottom is minus 14 degrees Celsius. "That means the lake's organisms have to deal with two extremes: the high salinity and the cold. Four species of archaea can cope with it, and they constitute almost 90 percent of the lake's total biomass," says Erdmann.

Erdmann isolates the viruses in the lake from samples that have been concentrated by using ultra-fine filters, so that the viruses can be studied in the laboratory. If typical bacterial viruses are transferred onto a petri dish covered with potential host cells, holes form in the bacterial lawn where the pathogens have destroyed the cells. However, many archaeal viruses do not destroy their host cells, but instead, bud off from the host cell like membrane vesicles. Therefore, Erdmann needs to maintain the cells in a liquid culture and then analyze the liquid for possible virus particles. Using this technique, she has discovered several unknown viruses so far.

Her discovery of a very specific virus-like particle raised her interest in particular. "We analyzed its genome and found that it wasn't a genuine virus, but a "plasmid" that can be transported in vesicles," explains Erdmann. Plasmids are circular DNA molecules from bacterial and archaeal cells that can be passed from one cell to another. In this way, they can rapidly spread important traits, such as antibiotic resistance, throughout a population. The function of most of the genes of the virus-like element are still unknown. However, some seem to be responsible for packaging the plasmid itself into a kind of membrane vesicle. "I think the particle we discovered is likely to represent an intermediate form between a plasmid that

PHOTO: SUSANNE ERDMANN/MPI FOR MARINE MICROBIOLOGY

Lake Tyrrell is a naturally occurring saline lake in southeastern Australia. It is an El Dorado for Susanne Erdmann, because almost 90 percent of the organisms living in it are archaea. In this environment, that is deadly to most other organisms, she has discovered unknown archaea and viruses so far.

by chance ended up in a vesicle and a virus that is actively engaged in this packaging process. So it could be an evolutionary precursor to a virus."

Means of transport for genes

Do viruses serve any purpose? "We suspect that viruses originally arose as very beneficial elements promoting exchange of information between cells. They distribute genes between organisms and thus generate diversity. Eight percent of the human genome, for example, is viral in nature. However, as soon as information is exchanged and organisms compete with each other, elements that replicate at the expense of others can also emerge. In this light, many of the viruses we see today that from our point of view seem to do nothing but harm their hosts probably represent an inevitable consequence of life." After her study of the inhabitants of Antarctica, Erdmann is now turning to the archaeal viruses from temperate latitudes, for example from the North Sea, in her research at the Max Planck Institute in Bremen. Compared to the difficulties in accessing Deep Lake, the project at first sounds more straightforward. In fact, it poses a different set of challenges, because the temperate seawater is home to countless microorganisms, unlike the icy lake in Antarctica. Just one to two percent of these are archaea, and it is precisely those that the researcher and her team need to locate and isolate.

In the coming years, Erdmann is planning to focus, amongst other things, further on the evolutionary history of viruses. "My dream is to find more viruses and virus-like elements that will help us better understand viruses," she says. That would enable her to tell the whole evolutionary story of the host and the virus – starting way back when the earth was still devoid of life.