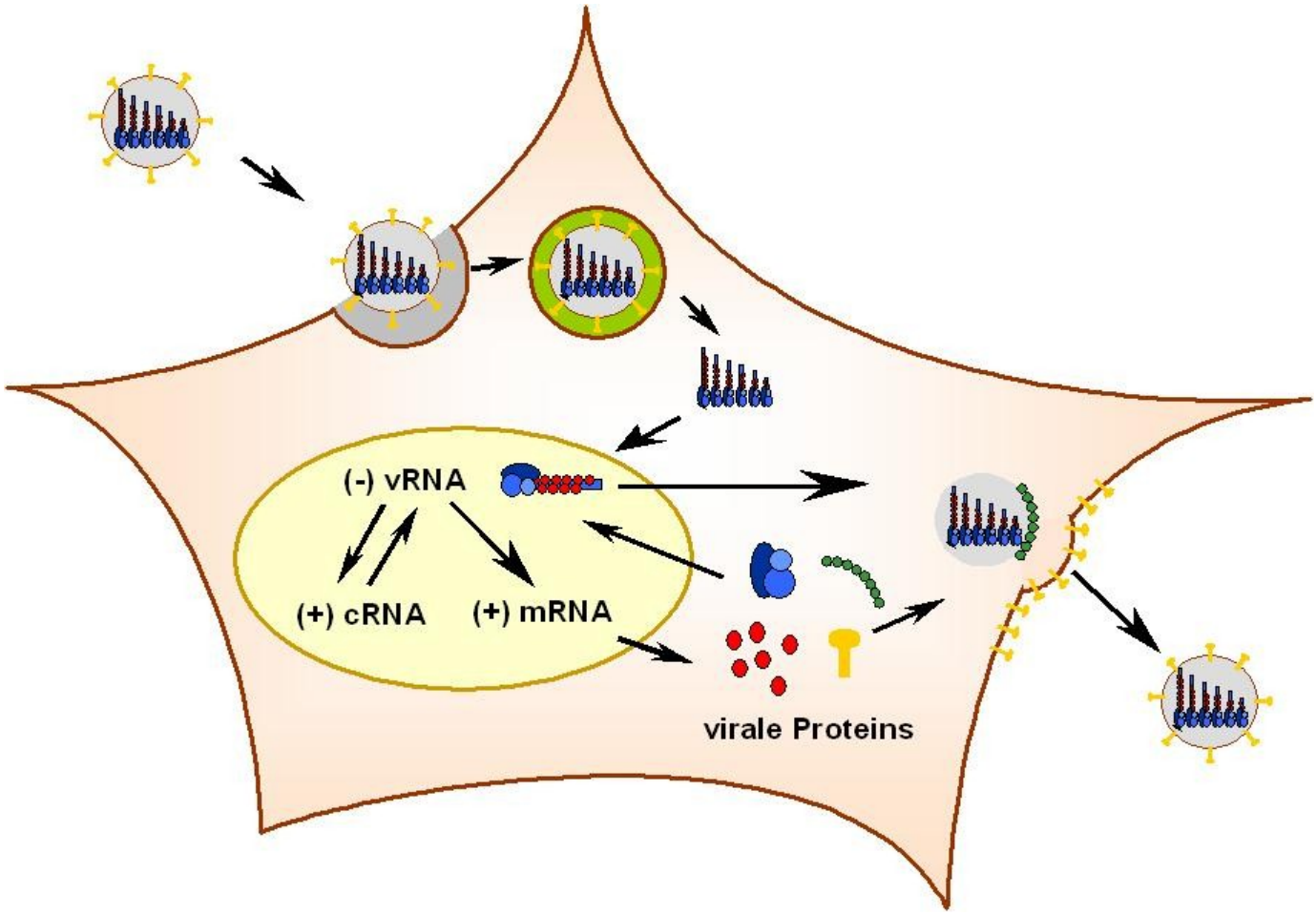
Trying to get a virus to reveal its tricks

The Thogoto virus is an exotic virus that presents virtually no danger to humans. Thogoto is related to the influenza virus, but is transmitted by tick bites rather than by coughing. A group of virologists led by Prof. Dr. Georg Kochs at the Freiburg University Medical Centre are using the virus as model system for its particular suitability in certain experiments. The group is investigating how the virus evades the antiviral defence of the infected host, a process that has some basic similarities to influenza viruses, although many differences become evident when the processes are looked at in detail. The researchers are also interested in how the host cells' defence strategies are able to control Thogoto virus infections. This research might open up potential strategies for new therapies for the treatment of viral influenza, as currently used drugs are far from perfect. The scientists' work with the Thogoto virus is broadening the basic theoretical and practical understanding of the interaction between pathogens and infected hosts.

Thogoto viruses and influenza viruses belong to the orthomyxovirus (previously known as myxoviruses) family of viruses. These two viruses have an RNA (ribonucleic acid) genome consisting of several segments, also known as segmented genome. In contrast to influenza viruses, the Thogoto virus does not appear to be dangerous for humans. It mainly infects rodents and farm animals. However, the researchers are not counting on this always being the case given that the coronaviruses were regarded as relatively harmless prior to the outbreak of the SARS epidemic eight years ago. Given that there was little knowledge of the effect and treatment of coronavirus, countries affected by SARS were unable to effectively combat its spread in Asia. "We are particularly interested in the Thogoto virus because, despite its similarities to influenza viruses, it transmits in a different way as well as having different replication mechanisms," said Prof. Dr. Georg Kochs from the Institute of Medical Microbiology and Hygiene at the Freiburg University Medical Centre. "I am sure that these differences can also be found on the molecular level. Additionally, they might be able to help us to gain a broader understanding of the molecular biology of influenza viruses."

Trick and counter-trick

Both the differences between Thogoto viruses and influenza viruses as well as their common features are hugely important in the search for answers. First the differences: When they enter their host cells, orthomyxoviruses activate a cascade of reactions that lead to the transcription of genes encoding interferon. The infected cells secrete interferon which induces an antiviral defence reaction in the neighbouring cells, thereby keeping the spreading virus in check. During evolution,



Replication of a virus in its host cell: The virus enters the cell and the genetic material enters the cell nucleus where numerous copies are generated. The genetic material is packaged into viral particles as it leaves the cell nucleus. After leaving the cell it can infect other cells.

the viruses have adapted to the strategy of their host cells. An influenza virus protein (NS1 protein) inhibits an alarm cascade shortly after a virus has entered a cell, with the result that the cell does not recognise the presence of the virus and stops producing interferon. This brings the defence reactions to a standstill. As Dr. Kochs and his team were able to show several years ago, the Thogoto virus has developed a different strategy. The Freiburg researchers discovered the ML protein, which is a modification of a viral structure protein that is normally responsible for packaging new viral particles. The ML protein exerts its effect in the relevant host cell. "It appears that this process influences a subsequent step in the defence cascade," said Dr. Kochs.

Detailed investigations of the process showed that ML binds to the TFIIB transcription factor. Normally, this molecule attaches to the promoter sequences of genes, together with other molecules, thereby initiating the transcription of these genes. However, ML prevents this from happening. The inhibition of transcription through ML is highly selective, affecting mainly interferon genes. The Thogoto virus strategy is therefore a specific blockage of the interferon-induced defence which takes place on a different level than that used by influenza viruses. The virologists are now interested in elucidating the exact mechanism that underlies this blockage. "Why is it only interferon genes that are affected, and not other genes, even though ML blocks a general transcription factor?" asks Dr. Kochs. The researchers have found a possible reason why. They discovered that ML also interacts with so-called interferon response factors, molecules that are also of crucial importance in the activation of interferon genes. Dr. Kochs and his team assume that these molecules specifically attract ML and cause it to interact with the interferon promoter,

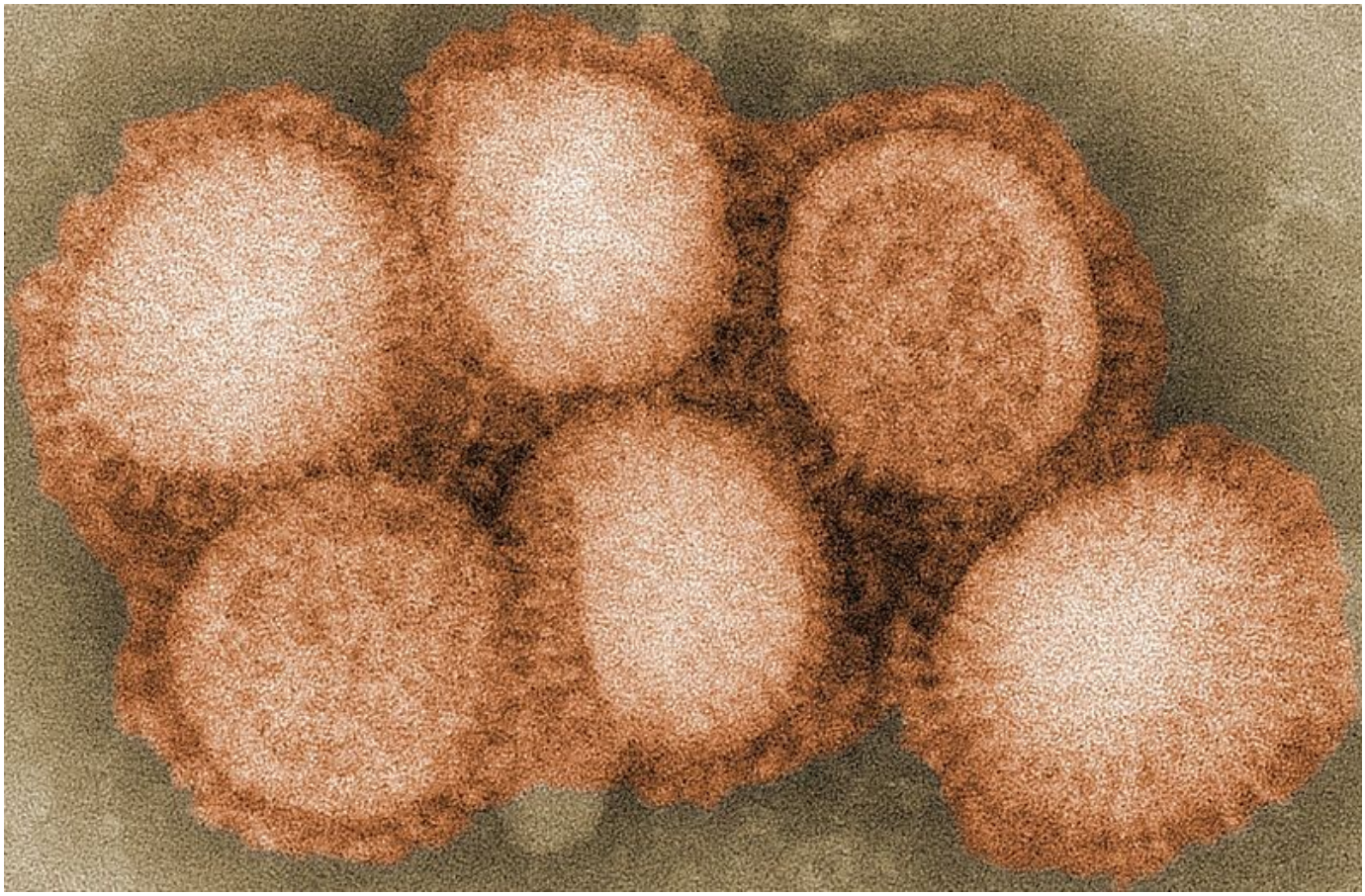
so it is only this promoter that has its normal function disturbed.

New therapeutic approaches against influenza viruses?

The experiments carried out by Kochs and his team focusing on Mx proteins (Mx stands for myxovirus resistance) show that despite all the differences between Thogoto and influenza viruses, the similarities between Thogoto and influenza viruses can help them gain useful insights. Mx proteins are formed when cells are stimulated by interferon. They prevent viruses from multiplying. “Of all viruses, the Thogoto virus is the virus that is the most sensitive to human Mx protein,” said Kochs. “For this reason, the Thogoto virus is important in the clarification of the antiviral mechanism.” Mx proteins prevent a crucial step from taking place during the replication of viruses. They inhibit the viral enzyme RNA polymerase that copies the genetic material of the viruses. In the cell nucleus, RNA polymerase, other proteins and the viral RNA genome form a complex known as ribonuclein protein complex (RNP). But how do the Mx proteins manage to block this complex?

Mx proteins are molecular machines that assemble into highly complex rings, thereby exerting a mechanical force on other molecules. Dr. Kochs and his team assume that the Mx protein rings surround the RNP complex, thereby preventing this complex from exerting its proper function. The researchers hope to carry out experiments to provide further evidence for this model. However, they have to overcome the problem that the molecular structure of Mx proteins is still not known despite many years of intensive research. Researchers at the Freiburg Department of Virology and a group from the Max Delbrück Centre in Berlin, with whom the Freiburg researchers work closely, have come a step further towards elucidating the structure of Mx proteins. In a recent publication in the journal Nature, the cooperation partners described the atomic structure of a segment of the human Mx protein and showed that the interaction between Mx proteins and RNP complex is crucial for the antiviral function of the defence molecule. “How does the recognition of viral RNP complexes work on the molecular level?” asks Dr. Kochs.

Future experiments will shed light on this and the Thogoto virus will play a crucial role in the researchers' investigations, in particular because it can be effectively inhibited by the Mx proteins. The researchers now hope to gain detailed insights into the way Mx proteins are able to fend off viruses. Moreover, they hope that this will help them move towards the development of new molecular therapies against influenza viruses. New ideas are important because influenza viruses are able to adapt rapidly to currently used drugs. "It's not the same for Mx proteins," said Dr. Kochs. "Although we have tried for many years to cultivate resistant viruses for laboratory purposes, it seems to be impossible." Will it be possible some time in the future to develop a therapy based on the Mx inhibition mechanism that will finally provide a way to defend the organism against influenza viruses?



Influenza viruses under the electron microscope.
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Model organisms