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Oops! Why mistakes make flu dangerous

Aartjan te Velthuis

Every autumn and winter we get infected with influenza viruses, the causative agents of flu. Typically, these viruses cause a very mild disease and if you are vaccinated and healthy you may not even notice them. On the other hand, infections with pandemic influenza viruses, such as the virus that caused the 1918 Spanish Flu, are far more dangerous and potentially lethal. In my group we have tried to find out why.

Influenza viruses infect our cells in order to copy their genetic information, which consists of eight ribonucleic acid (RNA) molecules. Unlike our own RNA, which is usually single-stranded and has a specific end called a '5' cap', the influenza virus RNA genome contains 5' triphosphates and partially double-stranded ends. This difference is sufficient to allow receptors inside of our cells, such as RIG-I, to detect influenza viruses and trigger warning signals. These warning signals, called cytokines and chemokines, alert neighbouring cells and shut down essential processes, preventing the virus from spreading. In the laboratory, we can perform experiments to investigate how well influenza viruses are detected by human cells. One such experiment relies on replacing the coding information of a key cytokine gene with the sequence of a luminescent protein. As a result, every time the cell wants to make this cytokine, we see the cell light up.

A key difference between infections with mild and dangerous influenza viruses is that the level of cytokine and chemokine production is usually low in mild infections and high in infections with dangerous viruses. This may sound counterintuitive because a strong immune response normally protects us. An infection in your leg, for instance, might cause a painful swelling but this immune response will help clear the infection and normally resolves without doing further harm. However, a strong immune response in our lungs (**Figure 1**) is dangerous, because a swelling there involves an accumulation of immune cells and fluids in our lungs, which may lead to suffocation.

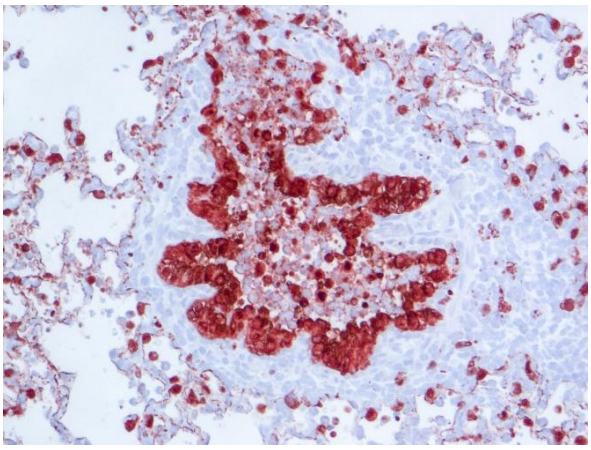

Figure 1. Bronchiole of lung with the 1918 flu virus. Infected cells are stained red. Credit Jurre Siegers, Debby van Riel, and Emmie de Wit from the Erasmus Medical Centre.

To find out why dangerous influenza viruses cause a strong immune response in our lungs, in my laboratory we investigated what lung cells "see" during infections by placing a tag on RIG-I that allows it to bind to a magnetic bead. Next, we opened up infected cells and used a magnet to "fish" out the RIG-I-RNA complexes from the cells. Interestingly, we found that RIG-I had bound to faulty influenza RNA molecules.

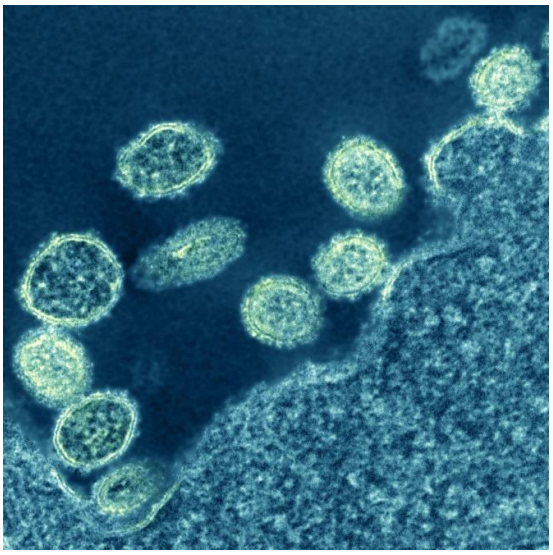

Figure 2. 1918 Influenza virus. Image credit: NIAID/NIH.

The enzyme responsible for copying the influenza virus genome is called the RNA polymerase. The RNA polymerase normally copies the influenza virus genome by taking a flu RNA molecule as a template and synthesising a new one using the nucleotides Adenine, Guanine, Uracil and Cytosine. However, it can also make mistakes and insert an incorrect nucleotide into the new RNA or truncate the new RNA molecule. Using our magnetic bead experiment, we found that our immune system detects truncated influenza virus genomes really well. When we compared different influenza viruses, we found that the 1918 pandemic virus (**Figure 2**) produced more truncated genomes than other influenza viruses.

We also observed more luminescence when we put this RNA in our modified cells, suggesting that the production of RNA fragments by pandemic viruses leads to a deadly stimulation of the immune system. Thus, we now think that dangerous flu infections arise because lethal influenza viruses make too many mistakes. We can now use this information to identify viruses that are dangerous by screening them for their ability to make faulty RNA molecules. Moreover, we hope that we will be able to develop an antiviral drug that will prevent influenza viruses from making these molecules altogether.

Want to know more?

Te Velthuis *et al*., (2018) *Nature Microbiology* **3**:1234–1242. https://doi.org/10.1038/s41564-018-0240-5

Radio 4: https://www.bbc.co.uk/programmes/b0bkpjp5

AUTHOR PROFILE

Aartjan te Velthuis completed his PhD at the University of Leiden, Netherlands, and then undertook a post-doctoral fellowship at the University of Oxford, UK. He is currently a Wellcome Trust Sir Henry Dale Fellow and Group leader at the University of Cambridge. His group works on influenza virus RNA polymerase, and how it contributes to the virulence of pandemic and highly pathogenic avian influenza viruses.