

April 2006: Hemagglutinin

Influenza virus is a dangerous enemy. Normally, the immune system fights off infections, eradicating the viruses and causing a few days of miserable flu symptoms. Yearly flu vaccines prime our immune system, making it ready to fight the most common strains of influenza virus. But once every couple of decades, a new strain of influenza appears that is far more pathogenic, allowing it to spread rapidly. This happened at the end of World War I, and the resultant pandemic killed over 20 million people, more than twice the number of people that were killed in the war.

Target and Attack

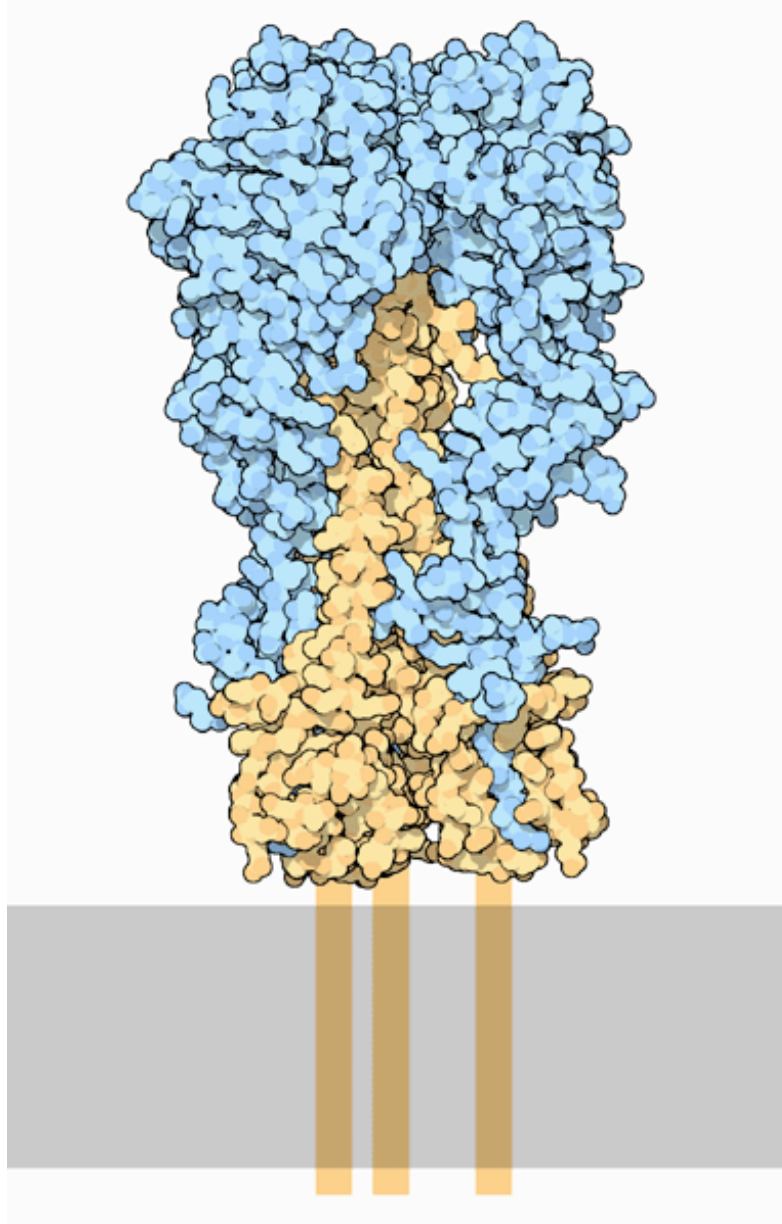
Hemagglutinin is one of the reasons that influenza virus is so effective. It is a spike-shaped protein that extends from the surface of the virus. In the active form, shown on the next page from PDB entry [1ruz](#), hemagglutinin is composed of two different types of chains, shown in blue and orange. The blue chains are the targeting mechanism: they search for specific sugar chains on our cellular proteins. When they find the proper one, hemagglutinin binds to the cell and the orange chains initiate the attack, as shown on the next page. The name hemagglutinin refers to the ability of influenza to agglutinate red blood cells: the virus is covered with many hemagglutinin molecules, which together can glue many red blood cells together into a visible clump.

Stealthy Subtypes

The specificity, and thus the danger, of each strain of influenza virus depends on the particular type hemagglutinin that it carries. Over a dozen subtypes of hemagglutinin are known. Three of these (termed H1, H2, and H3) attack humans--they specialize in finding the particular sugars in our respiratory tract, so the infection occurs there when we get the flu. Other subtypes, such as H5, attack proteins in the digestive system of birds. Most of these are not dangerous to us, and do not typically threaten the lives of the birds, so they exist as an invisible reservoir of virus. A potential danger occurs when these different strains start trading genes.

The H5N1 avian influenza virus that is showing up in the news is decimating bird populations, but it is not currently a danger to us since it doesn't have the right hemagglutinin to attack human cells (the N1 designation refers to the subtype of a second virus protein: neuraminidase). However, there is the possibility that it could acquire a human-specific hemagglutinin, and then it could cause real problems. One way for this to happen involves pigs. Pigs are susceptible to viruses of several subtypes, both the types that attack birds and the types that attack us. If a single pig gets infected with two different viruses at the same time, the viruses can shuffle and trade genes during the infection. This could potentially be a way to construct a virus with the virulence of the bird virus, combined with the ability to attack human cells.

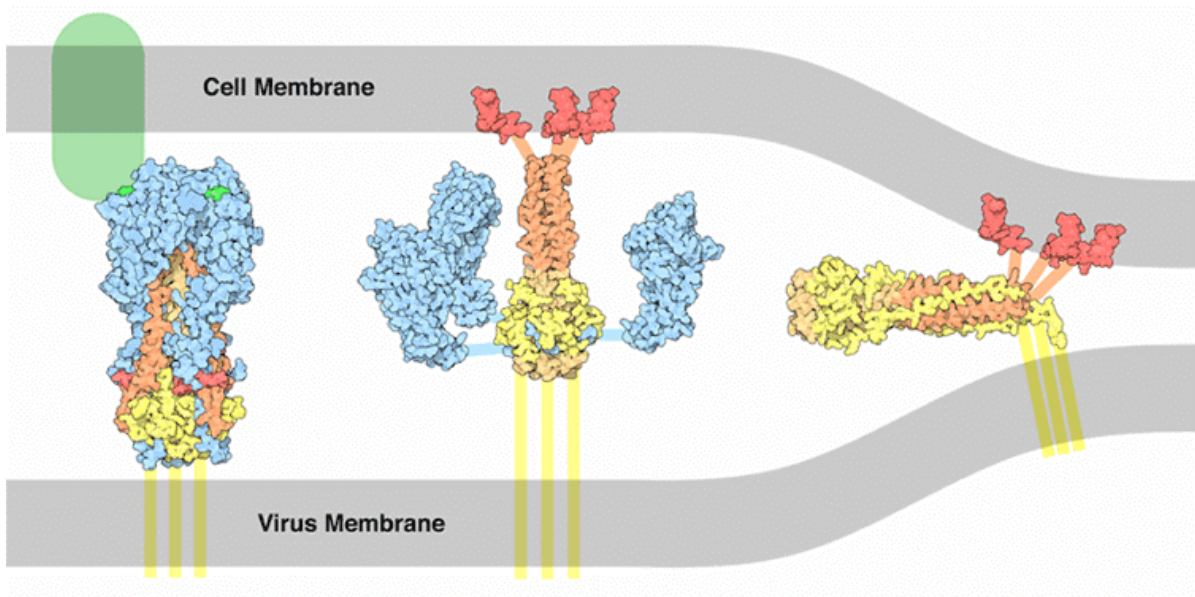
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Deadly Agent

The hemagglutinin shown here is taken from an actual virus of the pandemic that killed so many people in 1918. The DNA encoding this hemagglutinin was isolated from preserved samples, and the hemagglutinin was made in the laboratory according to this genetic information. Two crystal structures were obtained, the active form shown above (PDB entry [1ruz](#)), and a precursor form in PDB entry [1rd8](#). The protein is tethered to the virus membrane by a short segment of protein that is not seen in the crystal structure and is shown schematically on the next page.

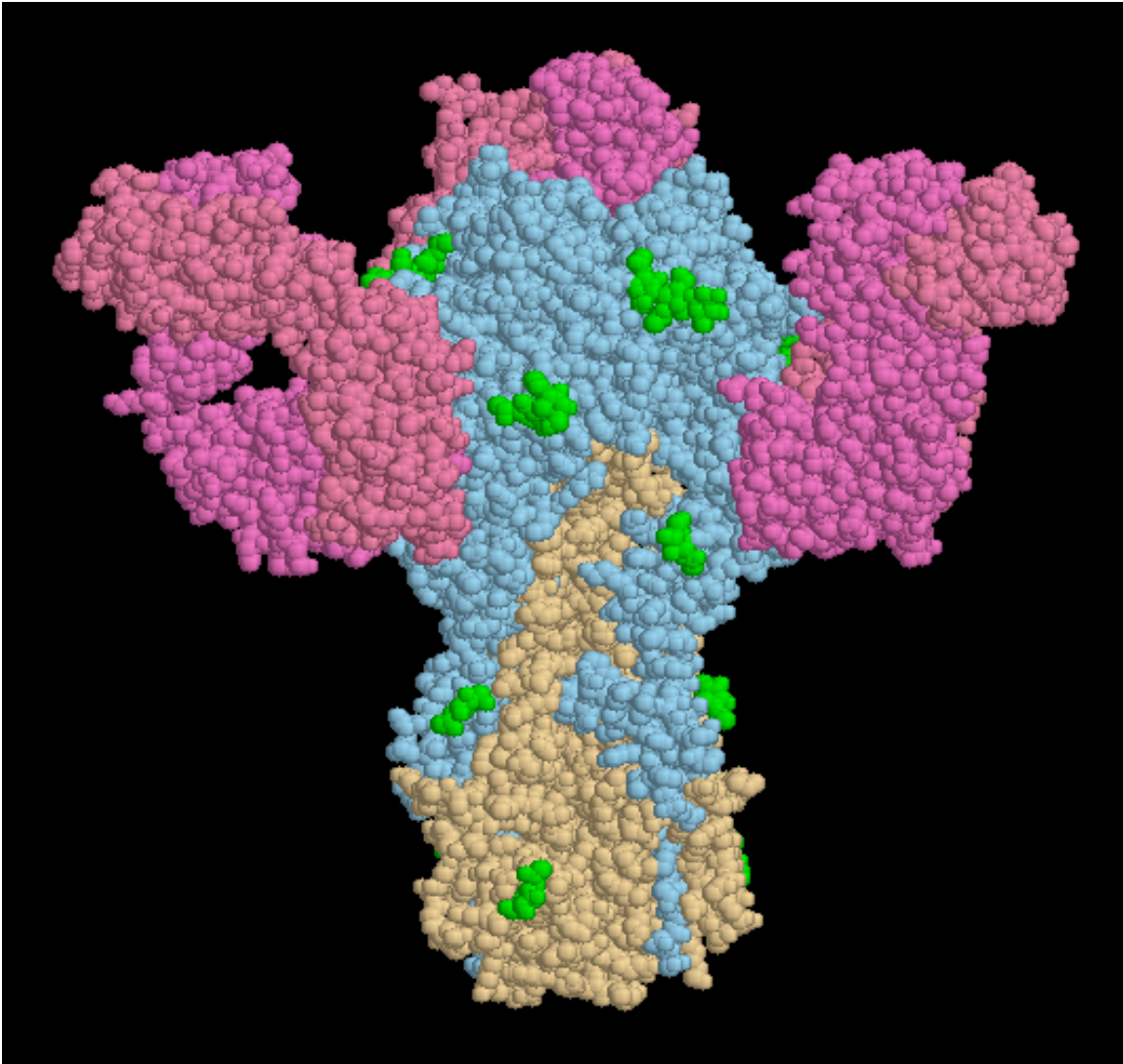
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Hemagglutinin in Action

Hemagglutinin is a deadly molecular machine that targets and attacks cells. This occurs in several steps. First, the three binding sites at the top of the spike bind to sugars on cellular proteins, shown in green at the top left (PDB entry [1hge](#)). Then, the whole virus is carried inside the cell into the endosome and the cell adds acid, which normally digests the stuff inside the endosome. But in the case of the virus, the acidic environment serves to arm the attack mechanism. In acid, hemagglutinin unfolds and then refolds into an entirely different shape. The portions shown in orange and red are normally folded against the protein, but in acid, they pop out and point upward, as shown in the center illustration (PDB entries [1htm](#), [1ibn](#) and [2vir](#)). The red portion, termed the fusion peptide, has a strong affinity for membranes, so it inserts into the cell membrane and locks the virus to the cell. Then, as shown on the left (PDB entry [1qu1](#)), the yellow portions zip up the side of the protein, pulling the two membranes close together. Finally, the new conformation of hemagglutinin somehow causes the two membranes to fuse--that part is still not well understood--and the viral RNA flows into the cell, starting the process of infection.

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Exploring the Structure

Antibodies are our first line of defense against influenza virus. PDB entry [1qfu](#) shows how one antibody attacks hemagglutinin, blocking it so that it cannot bind to cell surfaces. The structure includes hemagglutinin, shown in blue and orange, and three copies of a Fab fragment of antibody (Fab fragments are one arm from the Y-shaped antibody). Of course, viruses find ways of evading attack by antibodies, creating new strains that infect us each year. One way is to mutate the location of carbohydrate chains on the hemagglutinin surface. Several of these carbohydrates are shown in green here. If the virus adds a new carbohydrate at the location that the antibody binds, the antibody will no longer be effective.

This picture was created with RasMol.