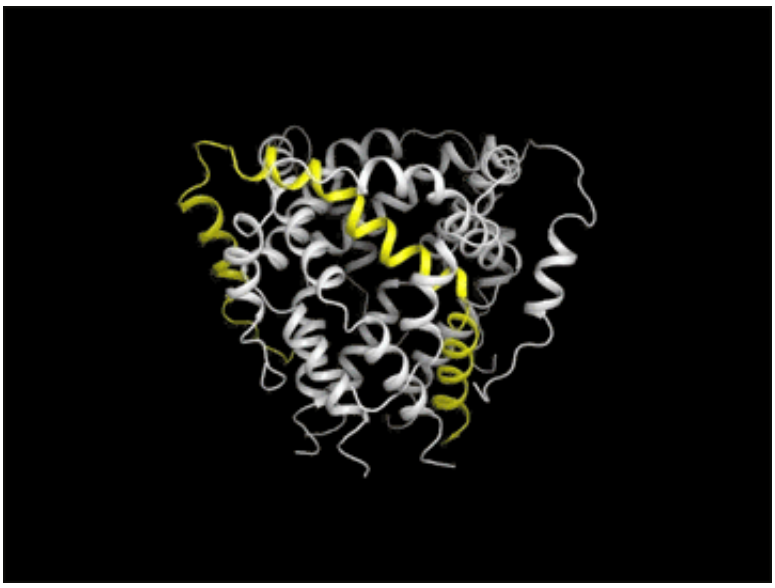
Seeing how the Hepatitis C virus builds ion channels could help researchers find new drugs to fight the disease

June 14 2013, by Jake Miller



The Hepatitis C virus's p7 ion channel is crucial to the assembly and release of infectious HCV viral particles. That makes it a tempting target for drugs to fight the disease. Credit: James Chou

(Phys.org) —Viruses are masters of minimalist design. With only a simple genome and a handful of proteins, a virus can hijack much more sophisticated cells and mimic many of the intra- and inter-cellular machinery built by their much more complex hosts. Using these same building blocks, many viruses—like Hepatitis C—can also make us dangerously ill.

The structures of viral architecture make a fascinating puzzle, one that may be key to understanding how drugs can break the infectious life cycle of a virus.

In findings published June 5 in *Nature*, James Chou, HMS professor of biological chemistry and molecular pharmacology, describes the structure of the Hepatitis C virus's p7 ion channel, a microscopic funnel that selectively permeates cations through biological membranes. This funnel is crucial to the assembly and release of infectious Hepatitis C virus (HCV) viral particles.

Chou's lab solved the high-resolution structure of the p7 ion channel and found the binding location for an influenza drug that has a surprising ability to block HCV.

"We were absolutely surprised by the highly unusual architecture adopted by this viral channel, which doesn't look anything like any of the known prokaryotic, eukaryotic or viral ion channels," Chou said. "We also found information that will be useful for immediate pursuit of new anti-HCV compounds targeting this viral channel."

Global clinical need

New drugs are desperately needed to combat HCV infection. Every year, more than 3 million people worldwide are infected with the virus, a blood-borne infection that targets liver cells. About 150 million people are infected and at risk of developing cirrhosis, which can lead to liver cancer. Every year, 350,000 people die from hepatitis C-related liver diseases.

There are six genotypes of the virus. Some strains of the virus respond well to the standard treatment regimen of interferon and ribavirin, but other strains have developed varying degrees of drug resistance. And as

an RNA virus—which has RNA as its genetic material instead of DNA—HCV makes copies of itself without the benefit of a genetic proof-reader. Like all RNA viruses, HCV is therefore capable of startlingly fast mutation and evolution. The virus can develop resistance to a drug in a single day. Researchers say it is crucial to develop multiple drugs that target diverse viral mechanisms in order to combat evolving resistance.

"To take out an RNA virus, whether it's flu or HCV, you need to find multiple targets and hit them all at the same time, using a cocktail approach. HCV currently has effective drugs targeting only a single type of target," Chou said.

Understanding viral membrane channels

In 2008 Chou's lab solved the structure of the M2 channel of the influenza virus, a viral channel that is the target of the 1960s-era anti-influenza drug rimantadine. The drug is a small molecule that blocks the M2 channel by fitting snugly inside the narrow channel and disrupts processes that are necessary for the virus's infectious cycle.

Clinical trials showed hints of promise for the use of rimantidine against HCV. It appeared that in several of the genotypes of the virus—including the strain Chou studied—the same drug also blocked the p7 channel built by HCV. Vexingly, in other strains it did not work at all.

Researchers were mystified. Not only are the two channels different sizes, they're also very different chemically. Chou suspected that understanding the physical structure of p7 would offer important clues.

The p7 protein is made of only 63 amino acids. The proteins used to build channels with similar function in bacteria have more than 200, and

even much longer in eukaryotic cells. Typically, in these higher-level organisms each protein in an assembled channel structure interacts with its nearest neighbors.

Chou found that to compensate for its small number of amino acids, p7 forms multiple links with neighboring molecules—and with the neighbors' neighbors—in order to form a stable structure with simpler raw materials. If the complex proteins of the eukaryotes are high-tech fibers with a perfect chemical mix to make a strong rope, the p7 channel is more like a simple cotton rope that gains strength from a clever, intricate braiding pattern.

"Viruses are known for their minimalist solutions to the challenges that they face. With such short genomes, they need to do more with less," Chou said. "This multi-molecular linking is a great way to optimize stability in a simple structure."

Chou's lab used state of the art Nuclear Magnetic Resonance techniques to analyze the p7 channel in solution as opposed to the crystallized state required for x-ray diffraction. This enabled Chou's team to observe the dynamics of the system as it shifts between the open and closed states of the channel. This "breathing" is crucial to the functioning of the channel. When the channel "exhales" it allows ions to pass across the membranes in key organelles located in the host liver cells.

Finding the binding

Chou's lab also identified the drug binding site for rimantidine or amantadine in p7, which is completely different from the binding mode in the influenza M2 channel. It turns out to be crucial to the functioning of the drug mechanism or rimantidine. While the tiny M2 channel in influenza gets plugged up by the drug molecule, in p7 the drug nestles into a series of pockets within a folded outside edge of the funnel. When

the drugs are in those pockets, the channel is unable to "exhale" and thus release ions.

"It's important to look at the chemical, electrical and mechanical aspects of this structure as parts of a dynamic system," Chou said. "Once we know the structure of the channel and can visualize how the system works together, we can begin to think about other ways to block its function, and perhaps use those insights to develop new drugs for HCV."

More information: www.nature.com/nature/journal/ … ull/nature12283.html

Provided by Harvard Medical School