Features of replication suggest viruses have common themes, vulnerabilities

August 14 2007

A study of the reproductive apparatus of a model virus is bolstering the idea that broad classes of viruses - including those that cause important human diseases such as AIDS, SARS and hepatitis C - have features in common that could eventually make them vulnerable to broad-spectrum antiviral agents.

In a study published today (Aug. 14) in the online, open-access journal *Public Library of Science Biology*, a team of researchers from the Howard Hughes Medical Institute (HHMI) at the University of Wisconsin-Madison describes in fine detail how an RNA virus known as flock house virus co-opts a cell's membranes to create an intracellular lair where it can safely replicate its genes.

The results provide strong evidence that at least some of the machinery four of the seven distinct classes of known viruses use to reproduce have common attributes. Such a discovery is important because it reveals a common viral theme that may be vulnerable to disruption and could lead to the development of drugs to treat many different kinds of viral infections, much like antibiotics are used to attack different kinds of bacterial pathogens.

"It turns out that viruses previously thought of as distinct share common features," says Paul Ahlquist, an HHMI investigator and virologist at UW-Madison. "We've found some features of replication that appear to cross over among many viruses."

Using powerful electron microscopy techniques, Ahlquist's group and their collaborators made the first three-dimensional maps of a viral replication complex using flock house virus, which, like all viruses, requires a host cell to make new genetic material and maintain the chain of infection.

In the case of flock house virus, the Wisconsin group found, the virus co-opts intracellular membranes of mitochondria, critical energy-regulating structures found in most eukaryotic cells.

Squeezing into the space between the inner and outer membrane of the double-lined mitochondria, the virus creates tens of thousands of protein-lined, balloon-like pockets where it can make new copies of the viral genome while safe from surveillance and defense mechanisms of the host.

" The virus has developed a very elegant strategy," says Ahlquist. "It creates for itself a new compartment for RNA synthesis, where it can collect its (constituent) components, organize successive steps of replication, and sequester these steps from other processes in the cell, most importantly, host defense responses."

In essence, the virus is reorganizing the cell to make a new intracellular architecture for its own purposes, according to Ahlquist. "The virus is reorganizing the cell to make a new organelle. It is a way to keep out competing processes and alarm-ringers and have a place where it can carry out its processes efficiently and for long periods of time."

The balloon-like sacs or spherules observed by Ahlquist and his colleagues all had narrow necks that transcended the membrane of the organelle to the cytoplasm, the medium inside the cell and in which the organelle is suspended. The neck is a gateway that appears to permit substrates needed for replication to enter and newly made viral genomes

to exit.

The virus begins to co-opt the cell as a critical viral protein and viral RNA localize to the budding organelles, Ahlquist explains. "The virus takes over most of the available membrane. The protein creates a shell inside the spherule" to provide stability, and it is this use of a protein shell in replicating viral genes, the Wisconsin virologist suggests, that could be one of several common themes among different groups of viruses.

"Multiple features in the structure and function of these replication compartments appear similar across several virus classes," says Ahlquist. "This includes ways in which cell membranes are used to organize virus replication."

The shared features extend to most RNA viruses and a group known as reverse transcribing viruses, which include retroviruses such as HIV, suggesting a possible evolutionary link from a common ancestor.

Source: University of Wisconsin-Madison