

MARCH 23, 2002

Unexpected Links Found Between Many RNA Viruses

Howard Hughes Medical Institute researchers have discovered surprising parallels in the way that three different classes of RNA viruses replicate. The discovery suggests that there might one day be a common strategy to kill many different RNA viruses, a group that includes HIV, rotavirus, hepatitis C and polio viruses.

In an article published in the March 2002, issue of the journal *Molecular Cell*, HHMI investigator [Paul Ahlquist](#) and colleagues at the University of Wisconsin at Madison described the parallels among "positive-strand" RNA viruses ([+]RNA), retroviruses and double-stranded RNA viruses. Since these viruses cause a broad range of diseases, the scientists believe that identifying a common link between the viruses may be the first step to devising more general virus control or treatment strategies.

Positive-strand RNA viruses first copy their RNA genome into a negative-strand intermediate RNA before replicating their RNA. These viruses cause hepatitis C, encephalitis, hemorrhagic fevers, polio, foot and mouth disease, the common cold, and many other illnesses.

"Over the long term, understanding that these viruses share common properties should enable new antiviral strategies, and allow strategies developed for one type of virus to be generalized to the others."

- Paul Ahlquist

Retroviruses and other reverse-transcribing viruses, which include HIV and hepatitis B, copy their RNA into DNA before replicating their genome back into RNA. Double-stranded RNA viruses -- which include the rotavirus that kills about one million children a year in developing countries -- separate their strands and copy one strand to replicate.

Ahlquist and his colleagues discovered that, although the viruses seem to take distinct routes to replication, all three types use related pathways and structures to replicate their genes. By linking three of the six major classes of viruses, the results offer a significant unification within the field of virology.

“The multiple functional parallels we have found in replication mechanisms reveal unexpected links among these viruses,” said Ahlquist. “Recognition of these links means that principles learned from a variety of virus systems can be used to illuminate many others, allowing integration and generalization of knowledge across a wide range of important viruses. Among other benefits, this should facilitate improved strategies for virus control.”

Ahlquist and his colleagues based their insights on studies of a model [+]¹RNA virus called brome mosaic virus (BMV), which they induced to infect yeast. In studying BMV replication in yeast, Ahlquist and his colleagues examined the function of two proteins -- called 1a and 2a polymerase -- which are important in viral replication. Their electron microscopy of labeled viral components, and additional genetic and biochemical studies, revealed that large numbers of 1a proteins form partially budded spherules containing the viral RNA and 2a polymerase, which is responsible for replicating the viral RNA. These spherules are formed in the membranes of an internal cell structure called the endoplasmic reticulum, which is the site of BMV viral replication.

Their studies also showed that this [+]¹RNA replication machinery strongly paralleled that of retroviruses. In retroviruses, a protein called Gag forms a similar budding structure called a capsid that envelops the viral RNA and the Pol enzyme -- a reverse transcriptase that copies RNA to DNA. These capsids are formed in a structure called the plasma membrane, where retroviral replication takes place. This replication machinery is triggered by an RNA packaging signal that parallels the action of the signal in BMV.

These same principles of sequestering a viral RNA intermediate and its polymerase, plus other features of [+]¹RNA viruses, are shared with double-stranded RNA viruses, Ahlquist said.

According to Ahlquist, their findings and complementary findings of other scientists suggest that all three classes of viruses evolved from a common ancestor. For example, he said, besides the parallels he and his colleagues have just discovered, RNA replication in both retroviruses and BMV is “primed” by a specialized RNA called tRNA.

“We do not want to suggest that these discoveries will yield new treatments for viruses tomorrow,” he said. “However, over the long term, understanding that these viruses share common properties should enable new antiviral strategies, and allow strategies developed for one type of virus to be generalized to the others.