Penn researchers discover new mechanism for viral replication

August 16 2007

Researchers at the University of Pennsylvania School of Medicine have identified a new strategy that Kaposi's Sarcoma Associated Herpesvirus (KSHV) uses to dupe infected cells into replicating its viral genome. This allows the virus to remain virtually undetected by the body's immune system. Previous work suggested KSHV needed viral proteins to initiate replication, but this is the first study to directly show that a section of viral DNA can independently draw upon proteins within a host cell to promote its own replication. The study was published in the August issue of *Cell Host and Microbe*.

"Without the necessary production of a viral protein, the virus goes unidentified by the immune system while utilizing the host cell's replication machinery," explains lead author Erle Robertson, PhD, Professor of Microbiology and Director of Tumor Virology Training at Penn's Abramson Cancer Center. Specifically, KSHV can overwhelm a weakened immune system, resulting in the development of Kaposi's sarcoma and other diseases of the lymphocytes.

A virus, comprised of only its genetic code wrapped in a protective protein cover, will infect a cell by penetrating its membrane and releasing the viral genome into the cell. Because viruses are asexual, they are dependent upon the replication proteins, or "machinery" of host cells to make new copies of their DNA material. To access the cellular proteins needed to replicate, Robertson says most scientists believed viruses must produce a viral protein.

“Our findings now break the long standing dogma of the virology field, which held that tumor viruses associated with human cancers do require a viral protein to bind and initiate replication,” notes Robertson.

In the Robertson lab, previous studies of human cells infected with KSHV led researchers to locate a gene that codes for a viral protein called latency-associated nuclear antigen (LANA) that binds to viral DNA, signaling initiation of replication. To test whether or not KSHV replication was solely dependent upon LANA, the researchers eliminated the production of LANA by KSHV and introduced the LANA-free expression system into host cells. With viral protein production eliminated, the researchers discovered that KSHV DNA was capable of recruiting the cellular replication machinery proteins and so autonomously replicate.

“Once again, a virus has broken the mold in terms of our understanding of cellular processes and is teaching us new tricks about their ability to utilize the cellular mechanism for replication,” says Robertson. “By studying how viruses usurp this cellular function to their advantage, we can learn new bits of information about the mechanism of cellular replication in humans.”

In the future, Robertson and others plan to explore whether or not other viruses are capable of replicating without utilizing the role of viral proteins and learning more about cellular events that trigger replication. Also, researchers will look to identify ways to block KSHV from replicating without blocking cellular replication in order to stop the virus before it has a chance to overwhelm the immune system and progress into a disease.

Source: University of Pennsylvania School of Medicine