Cell biologist pinpoints how RNA viruses copy themselves

May 28 2010

Nihal Altan-Bonnet, assistant professor of cell biology, Rutgers University in Newark, and her research team have made a significant new discovery about RNA (Ribonucleic acid) viruses and how they replicate themselves.

Certain RNA viruses - Poliovirus, Hepatitis C virus and Coxsackievirus - and possibly many other families of viruses copy themselves by seizing an enzyme from their host cell to create replication factories enriched in a specific lipid, explains Altan-Bonnet. Minus that lipid - phosphatidylinositol-4-phosphate (Pl4P) - these RNA viruses are not able to synthesize their viral RNA and replicate. The key structural components on cell membranes, lipids often serve as signaling molecules and docking sites for proteins.

Viral replication is the process by which virus particles make new copies of themselves within a host cell. Those copies then can go on to infect other cells. An RNA virus is a virus that has RNA, rather than DNA, as its genetic material. Many human pathogens are RNA viruses, including SARS virus, West Nile virus, HIV, and the ones Altan-Bonnet has been studying.

As reported in the May 28, 2010 issue of *Cell,* Altan-Bonnet and her co-researchers for the first time have uncovered that certain RNA viruses take control of a cellular enzyme to design a replication compartment on the cell's membrane filled with PI4P lipids. Those lipids, in turn, allow the RNA viruses to attract and stimulate the enzymes they need for

replication. In uninfected cells, the levels of PI4P lipids are kept low, but in virally infected cells those levels increase dramatically. The findings by Altan-Bonnet and her colleagues not only open several possibilities for preventing the spread of various viral infections, but also may help to shed new light on the regulation of RNA synthesis at the cellular level and potentially on how some cancers develop.

"The goal of the virus is to replicate itself," notes Altan-Bonnet. "For its replication machines to work, the virus needs to create an ideal lipid environment which it does by hijacking a key enzyme from its host cell."

Altan-Bonnet and her team also were able to identify the viral protein (the so-called 3A protein in Poliovirus and Coxsackievirus infections) that captures and recruits the cellular enzyme (phosphatidylinositol-4-kinase III beta). Additionally, her lab was able to impede the replication process by administering a drug that blocked the activity of the cellular enzyme once it had been hijacked. Drug therapies to prevent viral replication potentially also could be targeted to prevent the hijacking of the enzyme.

Once that enzyme is hijacked, cells are prevented from normally operating their secretory pathway, the process by which they move proteins to the outside of the cell. In many cases, the impeding of that process can result in the slow death of the cell, leading to such problems as cardiac and vascular complications in those infected with the Coxsackievirus and neurological damage in those with Poliovirus.

Utilizing their recent findings, Altan-Bonnet and her team now plan to investigate PI4P dependence in other viruses as well as the role other lipids may play in different virus families. For example, the SARS virus also requires a lipid-rich environment for its replication, so her lab now is working with SARS researchers on determining what lipid is necessary for that virus's replication. In addition, they will be examining the role of

lipids in regulating RNA synthesis in cells, potentially providing new insight into some of the cellular mutations that occur in cancer.

"Given that a lot of what we know about cellular processes historically comes from the study of viruses, our studies may provide insight into the novel roles lipids play in regulating the expression of genetic material in cells," notes Altan-Bonnet.

Provided by Rutgers University