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Lipid-modifying enzyme: New target for pan-viral therapeutics

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Three different disease-causing viruses -- poliovirus, coxsackievirus, and hepatitis C -- rely on their unwilling host for the membrane platforms enriched in a specific lipid, phosphatidylinositol 4 phosphate (PI4P) on which they can replicate, Rutgers University researchers said on Dec. 7, at the American Society for Cell Biology annual meeting in Denver.

The viruses carry proteins that enable them to gain access to the P14P lipid for replication. The proteins snare one of the host's own lipid-modifying enzymes, a Type III PI4-kinase (PI4-kinase), reported Nihal Altan-Bonnet, Ph.D., of Rutgers University.

The PI4-kinase may prove to be an excellent target for panviral therapeutics, Altan-Bonnet said. When the Rutgers researchers blocked this PI4-kinase, the invading viruses all ceased replicating, and their host cells survived.

The Rutgers group has extended its investigations to identify other viruses that might be vulnerable to this countermeasure.

Blocking the PI4-kinase was effective, Altan-Bonnet explained, because invading viruses require this enzyme to manufacture the P14P lipid for the platforms that they must set up on the host's membrane-bound organelles, which include the Golgi apparatus and the mitochondria.

The viruses can replicate only on cell membrane platforms enriched with the P14P lipid. To gain access to the lipid, the viruses employ a protein

that hijacks the cell's P14-kinase.

They then use it to generate the lipid that enriches the platform. Once established, the viruses rapidly make copies of themselves that go on to infect other cells in the organism.

In normal, uninfected cells, the level of PI4P lipid on organelle membranes is generally low and increases only when signaling and membrane-remodeling proteins are required by the cell, said Altan-Bonnet.

But in infected cells, levels of PI4P lipid dramatically increase, reflecting the viruses' need for more PI4P lipid-enriched membrane surface to anchor their replication machinery.

Altan-Bonnet's lab also found that these membrane surfaces are enriched with cholesterol as well as PI4P lipid. Normally, cholesterol regulates membrane fluidity and elasticity, generating domains to sequester proteins so they can interact effectively.

Altan-Bonnet said that the PI4P lipid and cholesterol together may generate "sticky" membrane domains that viruses exploit for replication. Since viral proteins are relatively few after they invade the host cell, a "sticky" rallying point could be critical to their survival.

The researchers also discovered that RNA polymerases, which are vital for synthesizing the nucleic acids of viruses, have specific binding sites that lock onto PI4P lipids.

More information: "Viral interior design: Rewiring the host to generate organelle platforms for replication," Wed., Dec. 7, 2011, 10:15 a.m. to 10:35 a.m., during Minisymposium: Cell-Pathogen Interactions (Viruses and Bacteria) Presentation: 180 Room: 605

Provided by Rutgers University