Dengue protein modulates human enzyme: Fuel for replication

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Dengue is a mosquito-borne tropical disease currently endemic in more than 10 countries. According to the World Health Organization, 390 million people are infected by dengue every year.

The disease can be caused by one of the four types of dengue virus transmitted by the *Aedes aegypty* mosquito, the main vector for dengue. In humans, symptoms of dengue infection include fever, headache, muscle and joint pain and a characteristic skin rash. In some cases, dengue infection can take a dangerous turn and develop into a life-threatening hemorrhagic fever and dengue shock syndrome.

A tetravalent vaccine that could protect against all four types of dengue virus is not available—and neither is one that could protect against a single type, for that matter. What is more, no specific treatment against dengue exists. Thus, researchers have sought strategies to reduce mosquito habitat or replication. Unfortunately, none of the approaches developed so far has been successful in eradicating the disease or diminishing the odds of being bitten by the mosquito.

NS1 is one of the seven nonstructural proteins composing the dengue virus and more specifically its replication machinery. It is an abundant protein detected in the serum of infected patients and used as a target for early detection. Without NS1 the virus cannot replicate whereas NS1 mutation decreases virus yield. Previous studies have suggested that NS1 binds to some of the host's proteins while others have pointed to a pivotal role for NS1 in virus replication. But what the NS1-binding protein is and why its role in replication is so crucial were questions waiting for answers.

Now a new study done by a group at the Institute of Biophysics Carlos Chagas Filho (IBCCF), at the Federal University of Rio de Janeiro (UFRJ), Technology Education Faculty of the State of Rio de Janeiro, and Laboratory of Computational Biology (FAETEC), National Institute for Metrology, Quality and Technology (INMETRO), in Rio de Janeiro, Brazil reveals new information on the role of NS1.

Using co-immunoprecipitation, a technique that detects protein-protein interactions through an antibody-containing resin that captures the primary target (in this case NS1), the group found that the viral protein that NS1 binds to is well-known to any cell biologist: Glyceraldehyde 3-phosphate dehydrogenase or GAPDH.

GAPDH is an enzyme involved in the cycle of glycolysis, which is the cell cycle that breaks down glucose to generate energy and carbon molecules. The enzyme is ubiquitous and very abundant in animal cells and is also involved in non-metabolic processes such as control of gene expression and trafficking of particles. Because GAPD is so abundant in the cell, the group also performed other complementing tests to confirm that the binding between NS1 and GAPDH is specific and not a spurious finding.

"As obligatory parasites, viruses rely on the host metabolism to obtain what they need to generate their progeny. In this study we show that in human cells, NS1 binds to GAPDH as a way to increase energy production to be used for viral replication," says Dr. Ronaldo Mohana Borges, who led the study. Indeed, energy production modulation is a remarkable feature that improves the energy supply required for supporting active viral replication.

The authors hypothesize that NS1 modulates the host metabolism by increasing GAPDH glycolytic activity early on in the course of infection and thus should be considered as an important target for the development of new drugs to treat dengue.

More information: The paper entitled "Dengue virus NS1 protein modulates cellular energy

metabolism by increasing glyceraldehyde-3-phosphate dehydrogenase activity" has been published in the *Journal of Virology* and can be found at this link: jvi.asm.org/content/early/2015 … 342-15.full.pdf+html

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