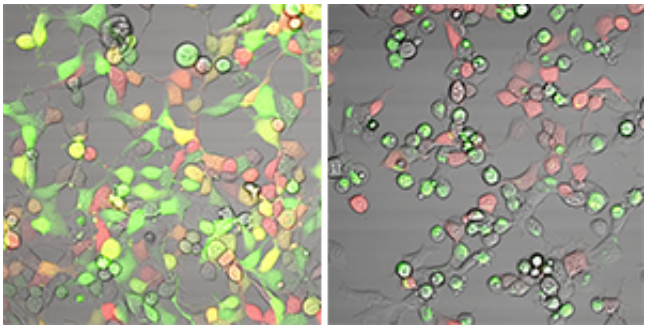
# Virology: Seeking solutions to viral migration

July 3 2013



Cultured cells (green) normally vulnerable to infection by chikungunya virus (red; left) acquire additional antiviral resistance after being genetically modified to produce the protein viperin (right). Credit: 2013 A*STAR Singapore Immunology Network

Although seldom fatal, persistent infection by chikungunya virus (CHIKV) afflicts patients with joint pain lasting months or even years. This insect-borne virus has received relatively little scientific attention in the 50 years since its initial description in African patients, but researchers in Singapore have now uncovered a host protein that can keep CHIKV in check.

"Globalization and climate warming have lent a helping hand in the resurgence of CHIKV, such that a virus originally from Africa and mosquitoes originally from Asia [could] meet in the Indian Ocean and spread to other parts of the world," explains Preston Teng, a researcher in Lisa F. P. Ng's laboratory, part of the A*STAR Singapore

Immunology Network. The expanding reach of the virus motivated Ng and her co-workers to investigate how CHIKV interacts with the immune system.

Ng's team had already established that CHIKV infection triggers cellular signaling pathways mediated by the type I interferon proteins, which activate genes involved in the antiviral 'innate' immune response. As a follow-up, the team searched for specific target genes activated in immune cells collected from 24 CHIKV patients. Their analysis revealed a sharp, viral load-dependent increase in the activity of the gene encoding the protein viperin, which is involved in the defensive response to numerous viruses.

Ng and co-workers showed that forced production of viperin conferred additional protection against infection upon a human cell line normally susceptible to CHIKV (see image). Conversely, genetically modified mice lacking viperin were prone to heavier viral loads following CHIKV infection, resulting in more severe inflammatory symptoms.

Viperin thwarts different viruses by distinct mechanisms, so the researchers carved the protein into pieces to identify which segment acts against CHIKV. Unexpectedly, they found that viperin's anti-CHIKV activity resides almost entirely within a single helical segment of the protein. "We were intrigued to find that a short, 42-amino acid fragment of viperin was sufficient to inhibit CHIKV infection and replication effectively," says Teng.

This domain helps to localize viperin to a specific cellular compartment known as the endoplasmic reticulum (ER), which contributes to the production of both host and viral proteins in infected cells. The researchers propose that viperin is capable of triggering a 'stress response' in the ER that effectively shuts down production of key viral components. This process could be exploited to bolster patient defenses

against CHIKV. In future research, Ng, Teng and colleagues plan to uncover the specific antiviral mechanism of this viperin domain.

**More information:** Teng, T.-S., et al. Viperin restricts chikungunya virus replication and pathology. *The Journal of Clinical Investigation* 122, 4447–4460 (2012). www.jci.org/articles/view/63120

Provided by Agency for Science, Technology and Research (A*STAR), Singapore

Citation: Virology: Seeking solutions to viral migration (2013, July 3) retrieved 4 May 2024 from https://medicalxpress.com/news/2013-07-virology-solutions-viral-migration.html

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