Dengue subgenomic RNA binds TRIM25 to inhibit interferon expression for epidemiological fitness

Gayathri Manokaran, Esteban Finol, Chunling Wang, Jayantha Gunaratne, Justin Bahl, Eugenia Z. Ong, Hwee Cheng Tan, October M. Sessions, Alex M. Ward, Duane J. Gubler, Eva Harris, Mariano A. Garcia-Blanco, Eng Eong Ooi

Dengue has become the most common mosquito-borne viral disease globally and more than half of the world’s population are at risk of infection each year. The error-prone replication of the dengue virus genome has also produced new genetic strains of dengue virus, some of which appear to spread more effectively through natural human-mosquito-human cycles, causing dengue epidemics. However, which mutation is important and how the mutation affects the virus’ ability to spread epidemically remains poorly understood.

To determine the mutations that affect dengue epidemics, we studied dengue viruses that emerged during the 1994 dengue epidemic in Puerto Rico. We showed that 3 mutations in the tail end of the dengue virus genome conferred the new strain of virus with a greater ability to evade human antiviral responses. Molecularly, the 3 mutations increased the formation of subgenomic RNA of the virus that directly binds and disables a human protein called TRIM25. TRIM25 plays a critical role in sustaining and amplifying the cellular signaling that induces the production of interferon which is our cell’s natural antiviral signal. With low levels of interferon, dengue virus propagates to higher levels in humans thereby increasing the likelihood that Aedes mosquitoes that bite a dengue case would spread the virus to new susceptible individuals.

This work thus not only identified a mechanism that enables dengue virus to infect humans more effectively, it also demonstrates how different scientific disciplines can be harnessed to identify a driving force of epidemics. By determining other driving forces of epidemics, we will be able to focus our public health resources on the source of the problem more effectively.

The full paper can be accessed via:

http://science.sciencemag.org/content/350/6257/217.full