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Researchers discover how dengue suppresses the human immune system

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Scientists have discovered a new pathway the dengue virus takes to suppress the human immune system. This new knowledge deepens our understanding of the virus and could contribute to the development of more effective therapeutics.

For years, the conventional approach to target the dengue virus was through vector control, which was regarded to be the most effective method. This is because the mechanics of the virus have been elusive, which in turn hampered the development of effective treatments and vaccines.

Fortunately a new study, published in the prestigious journal *PLOS Pathogens*, has given us fresh insight into the virus. Researchers from the Program in Emerging Infectious Diseases (EID) at Duke-NUS Graduate Medical School Singapore (Duke-NUS) have discovered a new way that dengue virus-2 (DENV-2) uses to evade the human defense system. Typically, when a virus enters the body and infects cells, it induces the production and release of interferons (IFNs), which are proteins that raise the bodies' anti-viral defense mechanisms.

The dengue virus enters the cell and produces large quantities of a non-coding, highly-structured viral RNA termed sfRNA, which is part of the genetic material of the dengue virus. The team found that sfRNA attaches itself to G3BP1, G3BP2 and CAPRIN1, proteins in the cell that typically help in producing antiviral proteins in response to IFNs. Because of this interaction, the cell is unable to mount its antiviral

defenses and protect itself against virus replication.

"These findings were surprising because in 30 years of RNA and dengue related research this new mechanism was never discovered," explained senior author Professor Mariano Garcia-Blanco from EID.

"We not only found a new way in which the pathogen (dengue virus) interferes with the host response (human immune system) we also uncovered the first mechanistic insight into how this non-coding RNA works. This discovery opens the door to explore therapeutics through this channel."

These findings highlight new steps that regulate our immune response, and in the case of dengue, how the virus has learnt how to avoid these defenses. It also highlights the differences between the four dengue strains and how more research is needed to understand this highly complex virus.

"The dengue virus employs multiple strategies to evade our immune responses. These strategies provide the virus with redundancies so that if one approach fails, it has others to provide it with the necessary means to thrive," commented Associate Professor Eng Eong Ooi, Deputy Director of EID.

"Prof Garcia-Blanco's lab describes a novel way in which dengue virus is able to avoid being killed by our antiviral response. It produces fragments of its own genome to act like a sponge to soak up those factors needed to produce the virus killing machinery. This work is an important contribution to our overall understanding of the evasive strategies employed by dengue virus, which is important for devising new and effective methods for treating dengue patients."