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Researchers in Hong Kong unravel key viral enzyme's mechanism targeting mosquito-borne viruses

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Providing a crucial foundation for designing drugs that can block the MTase enzyme



Developing effective antiviral drugs against mosquito-borne viruses like dengue and Zika requires understanding the function of their viral enzymes. Arising from the doctoral research of NG Lok Wan from the Department of Chemistry, Hong Kong Baptist University, Professor HAN Wei, Professor AIK Wei Shen and Professor CHENG Yuen Kit, and researchers from their labs have made a significant stride by investigating NS5-methyltransferase (MTase). This crucial enzyme helps orthoflaviviruses survive and replicate by modifying their RNA cap.

It has been a long-standing puzzle how GTP, a molecule mimicking the RNA cap, travels from its initial binding site to the enzyme's active centre for modification. To solve this, the team used advanced computer simulations to trace GTP's journey within the enzyme. Their simulations revealed multiple pathways through which GTP interacts with specific enzyme components, guiding it toward the catalytic centre. Even more remarkably, the simulations showed how the enzyme changes its overall shape to facilitate GTP's movement. This discovery explains previous perplexing observations where remote mutations influenced enzyme activity, offering fresh insights into how the enzyme's structure supports viral replication.

This research provides a crucial foundation for designing drugs that can block the MTase enzyme, potentially leading to new treatments for orthoflavivirus infections. By clarifying GTP's interaction with the enzyme, the study significantly advances understanding of viral enzyme function and showcases the power of computational approaches in visualising viral mechanisms to guide future drug development.