Modeling the Interaction Between Dengue Virus NS2B3 and Human cGAS

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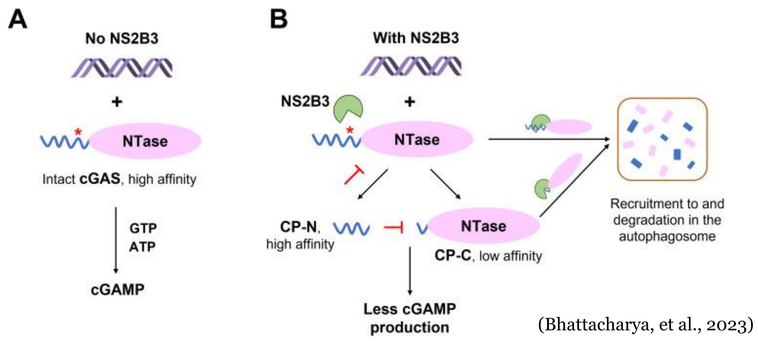
Abstract

The dengue virus (DENV) is a mosquito-transmitted human virus that has remained a significant public health threat. This virus has affected 50 million people worldwide and causes around 20,000 deaths yearly (WHO). To proliferate in the cell, DENV has found ways to bypass the immune response. The NS2B3 protease (consisting of NS2B and NS3) specifically interacts with the cGAS immune sensor to successfully stop the activation of the immune response. In this study, we used protein docking and visualization software to model potential NS2B3-cGAS interactions. These results provide a useful starting point for the experimental validation of NS2B-cGAS interactions, which will deepen our understanding of the disease and lay the foundation for future vaccine and therapeutic developments.



(Bhattacharya, et al., 2023)

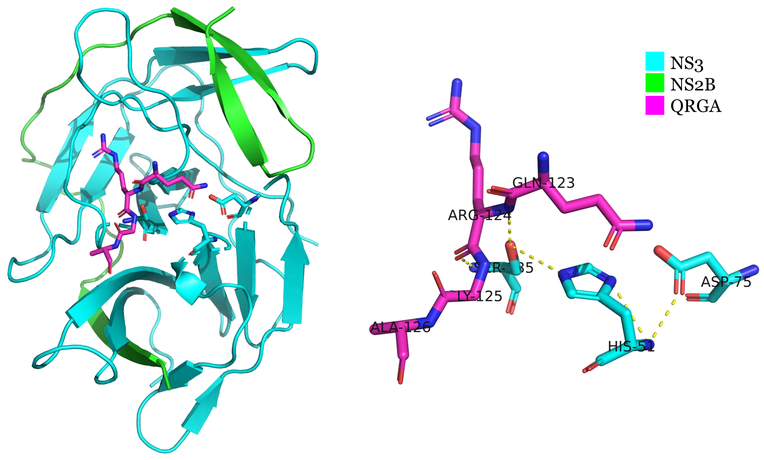
Introduction

- One strategy DENV uses to evade the human immune system involves the DENV NS2B3 protease complex, which cleaves the DNA sensor cyclic GMP-AMP synthase (cGAS) to inhibit the production of type I interferon, an anti-viral cytokine, via the cGAS-cGAMP-STING pathway (Aguirre, et al., 2017).
- Previous studies have elucidated the structures of DENV NS2B3 and human cGAS. It has also been shown that NS2B3 cleaves the N-terminus of cGAS at the major cleavage site 123QRGA126 and mediates the degradation of the C-terminus of cGAS via autophagosomes (Aguirre, et al., 2017; Bhattacharya, et al., 2023).
- However, the molecular interactions between the two proteins remain unknown. In this study, we use protein docking tools to predict possible NS2B3-cGAS interactions and analyze their plausibility using molecular visualization software, for the purpose of learning more about the dengue virus and aiding future vaccine and therapeutic developments.

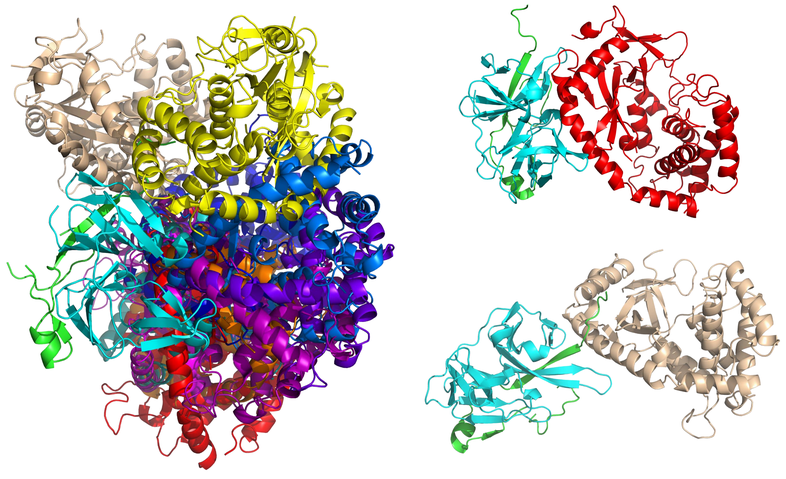
Methods

- A homology model of an unlinked NS2B3 protease bound to the QRGA peptide was generated using SWISS-MODEL and PyMol with structures of linked NS2B3 bound to aprotinin (3U1J) and unlinked Zika virus NS2B3 (5H6V) from the PDB database.
- ClusPro was used to dock linked NS2B3 (2FOM) to human cGAS apo form (4MKP).
- All resulting structures were analyzed with PyMol.

Results



The unlinked DENV NS2B3 homologous model bound to 123QRGA126 (left) and a closeup of the active site His51-Asp75-Ser135 (right). NS3 is shown in cyan, NS2B in green, and QRGA in magenta. Possible hydrogen bonds are shown in a yellow dashed line.



Left: the top ten models of NS2B3 and cGAS C-terminus generated by ClusPro superimposed on top of each other. Right: model 0 (top) and model 9 (bottom). In all models, NS3 is shown in cyan, NS2B in green, and cGAS in an alternate colors.

Discussion

- The unlinked NS2B3 model shows a different conformation than the linked NS2B3 structure.
- QRGA interacts with the active site through hydrogen bonding between arginine and serine in the catalytic triad.
- 8/10 models generated by ClusPro showed cGAS interacting with the active site of NS2B3 (His51-Asp75-Ser135), confirming that the active site not only plays a role in cleaving the N-terminus, but also in mediating the degradation of the C-terminus.
- Two out of the top ten models (3 and 9) show the C-terminus of cGAS interacting with the N-terminus of NS2B. This confirms previous experimental discoveries, but the significance of this interaction remains unknown.
- As this project is still being worked on, models and interactions regarding the N-terminus need to be generated and analyzed as well.
- Further experimental verification is needed to confirm the validity and importance of these computational models.

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