World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:14, No:06, 2020

Biophysical Characterization of the Inhibition of cGAS-DNA Sensing by KicGAS, Kaposi's Sarcoma-Associated Herpesvirus Inhibitor of cGAS

Authors : D. Bhowmik, Y. Tian, Q. Yin, F. Zhu

Abstract : Cyclic GMP-AMP synthase (cGAS), recognises cytoplasmic double-stranded DNA (dsDNA), indicative of bacterial and viral infections, as well as the leakage of self DNA by cellular dysfunction and stresses, to elicit the host's immune responses. Viruses also have developed numerous strategies to antagonize the cGAS-STING pathway. Kaposi's sarcoma-associated herpesvirus (KSHV) is a human DNA tumor virus that is the causative agent of Kaposi's sarcoma and several other malignancies. To persist in the host, consequently causing diseases, KSHV must overcome the host innate immune responses, including the cGAS-STING DNA sensing pathway. We already found that ORF52 or KicGAS (KSHV inhibitor of cGAS), an abundant and basic gamma herpesvirus-conserved tegument protein, directly inhibits cGAS enzymatic activity. To better understand the mechanism, we have performed the biochemical and structural characterization of full-length KicGAS and various mutants in regarding binding to DNA. We observed that KicGAS is capable of self-association and identified the critical residues involved in the oligomerization process. We also characterized the DNA-binding of KicGAS and found that KicGAS cooperatively oligomerizes along the length of the double stranded DNA, the highly conserved basic residues at the c-terminal disordered region are crucial for DNA recognition. Deficiency in oligomerization also affects DNA binding. Thus DNA binding by KicGAS sequesters DNA and prevents it from being detected by cGAS, consequently inhibiting cGAS activation. KicGAS homologues also inhibit cGAS efficiently, suggesting inhibition of cGAS is evolutionarily conserved mechanism among gamma herpesvirus. These results highlight the important viral strategy to evade this innate immune sensor.

Keywords : Kaposi's sarcoma-associated herpesvirus, KSHV, cGAS, DNA binding, inhibition
Conference Title : ICSEEE 2020 : International Conference on Structural Enzymology and Enzyme Engineering
Conference Location : New York, United States
Conference Dates : June 04-05, 2020