Innate sensing of picornavirus infection involves cGAS-STING-mediated antiviral responses triggered by mitochondrial DNA release

Liu, H., *et al*. *PLoS pathogens*. 2023; *19*(2): e1011132.

Presenter: Yi-Shiuan Hsu **Date/Time**: 2024/11/28, 16:10-17:00

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Background: Cyclic GMP-AMP synthase (cGAS) is a critical sensor in the innate immune response, particularly against DNA and RNA virus infections. While picornaviruses are known to inhibit host innate immunity through vRNA induced sensing of retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) pathways, their impact on cytosolic DNA sensors like cGAS remains unclear. Mitochondrial dysfunction during picornavirus infections is a potential trigger for mitochondrial DNA (mtDNA) release, which can activate the cGAS-stimulator of interferon genes (STING) signaling pathway.

Objective: To determine whether picornavirus infections, including enterovirus 71 (EV-A71), Seneca Valley virus (SVV), and foot-and-mouth disease virus (FMDV), activate the cGAS-STING pathway via mtDNA release and how picornaviruses antagonize this immune response.

Results: Picornavirus infections caused mitochondrial damage and mtDNA release both *in vitro* and *in vivo*, mediated by the viral 2B proteins. EV-A71 and FMDV triggered VDAC1-dependent mtDNA release via mitochondrial permeability transition pore (mPTP) opening, while SVV also involved Bak/Bax proteins. Released mtDNA bound to cGAS, activating an antiviral response. cGAS was essential for inhibiting virus replication through IFN-β production, deficiency would lead to higher mortality in infected mice. Furthermore, SVV 2C protein induced cGAS degradation via the autophagy pathway, while conserved amino acids Y155 and S156 in EV-A71, CA16, and EMCV 2C proteins inhibited cGAS-STING by interacting with STING.

Conclusion: Picornavirus infections activate the cGAS-STING pathway via mtDNA release. However the virus's 2C protein can antagonize the antiviral immunity mediated by this pathway. This study demonstrates novel strategies employed by picornaviruses to evade innate immunity and lays the groundwork for developing antiviral therapies targeting the cGAS-STING pathway.