Mitochondria F1-F0 ATP synthase facilitates dengue virus replication and serves as a potential target for developing antiviral agents

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Abstract

Aim of Study
Dengue virus (DENV) infection regulates mitochondria energy supply and homeostasis for the energy-consumed replication process. Mitochondria ATP F1-F0 synthase (ATP5B) plays a critical role in energy generation. The present study aims to investigate the involvement of ATP5B on DENV replication.

Materials & Methods
The effect of ATP5B on DENV replication was first determined by cell-based assay using human hepatoma Huh-7 and peripheral blood monocyte THP-1 cells. Those of effects were further confirmed using DENV-infected ICR suckling and AG129 mice in vivo. The specific inhibitor and short hairpin RNAs targeting signaling molecules were used to investigate the detailed mechanism by which ATP5B involved in DENV replication.

Results
We observed the elevated-ATP5B level in DENV-infected ICR suckling and AG129 mice. Based on cell-based experiments, we revealed that DENV infection can significantly induce ATP5B expression in Huh-7 and THP-1 cells. In addition, ATP5B gene silencing, overexpression of dominate negative mutation, or specific inhibitor oligomycin A resulted in suppression of DENV replication, suggesting that ATP5B is an important cellular factor contributing to DENV replication. Furthermore, we found that ATP5B gene silencing decreased the NF-kB- and AKT-CREB axis-mediated cyclooxygenase-2 (COX-2) expression through ATP-dependent AMP-activated protein kinase (AMPK) activation. In contrast, exogenous expression of COX-2 attenuated the antiviral effect of ATP5B gene silencing, suggesting that COX-2 is required for the ATP5B-mediated DENV replication. Notably, in ICR suckling mice model, we observed that oligomycin A can protect the mice from the strike of life-threatening DENV infection, suggesting that targeting ATP5B/COX-2 pathway could be a promising strategy against DENV infection.

Conclusions
ATP5B is an important factor for DENV replication and can serve as a potential target for developing therapeutic agents against DENV infection.

Keywords: Dengue virus; mitochondria F1-F0 ATP synthase; cyclooxygenase-2