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Hepatitis E virus triggers mitochondrial fusion to promote viral replication

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Background and Aims: Although hepatitis E virus (HEV) infection is generally self-limiting, severe complications and chronic hepatitis have been reported in special populations. Mitochondrial dysfunctions in hepatitis patients have been reported in many clinical studies. Liver cells contain abundant copies of mitochondria, and mitochondrial morphological dynamics, including the processes of fusion and fission, play important roles in physiology and pathogenesis. This study aims to understand mitochondrial morphological alteration in response to HEV infection and its implication in HEV replication.
Method: Liver biopsies of 17 patients with positive anti-HEV immunoglobulin (Ig) M and 5 control patients with hepatic hemangioma were reviewed for mitochondrial morphology by confocal immunofluorescent imaging. Human liver Huh-7 cells were used to model HEV infection *in vitro* and mitochondrial dynamics were observed by electron microscope and confocal immunofluorescent imaging. Lentiviral mediated RNAi was applied to silence genes that regulate mitochondrial dynamics. Viral replication was analyzed by quantitative real-time polymerase chain in reaction (qPCR).
Results: Immunofluorescent staining of liver biopsies showed that 11 out of 17 (65%) HEV infected patients presented aggregated and fused mitochondria; whereas mitochondria in all 5 uninfected control patients displayed uniform and spotty distribution. Ultrastructural analysis of HEV-infected Huh7 cells by transmission electron microscopy displayed elongated mitochondria (mitochondrial fusion) with obscure cristae. In contrast, mitochondria in uninfected cells displayed short and rod-like mitochondria with clear cristae. Consistently, confocal observation of HEV-infected cells by immunofluorescence substantiated tubular mitochondria, in contrast to dispersive and fragmented mitochondria in uninfected cells. Optic Atrophy 1 (OPA1) and mitofusion 1 (Mfn1) are the well-known positive regulators of mitochondrial fusion. In OPA1 and Mfn1 silencing cells, both the uninfected and HEV-infected cells presented fragmented mitochondria because of the impairment of the fusion machinery. Importantly, silencing of OPA1 or Mfn1 resulted in significant decrease of HEV RNA, suggesting that HEV-induced mitochondrial fusion facilitates viral infection. Further, exogenous mitochondrial dynamic regulator, ginsenoside Rg3 (G-Rg3), which had been reported to abrogate hepatitis C induced mitochondrial fission, was used to treat stable HEV infected cells. Importantly, G-Rg3 was able to promote HEV replication significantly.
Conclusion: HEV infection results in mitochondrial fusion which facilitates viral replication. Targeting mitochondrial dynamics represents a viable option for antiviral drug development against HEV.