Nature Reviews Microbiology | AOP, published online 10 June 2013; doi:10.1038/nrmicro3054

VIRAL PATHOGENESIS

Enabling HCV's need for fat

As part of its propagation strategy, hepatitis C virus (HCV) exploits host cell lipid metabolism pathways in infected hepatocytes, frequently resulting in pathological changes in lipid homeostasis. Liang and colleagues now identify an HCV-activated pathway involving inhibitor of NF-κB kinase subunit-α (IKKα) that modulates the host cell transcriptional programme for lipid metabolism genes and thus promotes viral particle production.

PhotoDisc/Getty

Following on from previous work, the authors noted that depletion of IKKα (part of the IKK complex, which regulates the antiviral NF-κB signalling pathway) markedly impaired viral particle production and secretion, and specifically assembly. Viral particle assembly is known to involve association of the HCV core protein with host lipid droplets; the authors observed that lipid droplet numbers increased following HCV infection and that depletion of IKKα abrogated this effect. Notably, silencing other NF-κB pathway components had no effect on lipid droplet formation and HCV assembly, indicating that IKKα-mediated induction of lipid droplet synthesis is NF-κB independent.

So, how does HCV activate IKKα? First, the authors identified the HCV 3′ UTR as the component that triggers IKKα-dependent signalling and consequent lipid droplet production. The 3′ UTR was shown to be specifically recognized by the host DexDH/H helicase DDX3X, a putative pathogen recognition receptor, which redistributed in the cytoplasm and colocalized with the 3′ UTR and IKKα. Importantly, the interaction between IKKα and DDX3X resulted in IKKα phosphorylation (and therefore activation) and translocation to the nucleus.

Sterol regulatory element-binding proteins (SREBPs) activate cholesterol and fatty acid synthesis and have been shown to be upregulated and activated in HCV-infected hepatocytes, so they might be involved in IKKα-mediated lipid droplet formation. Indeed, IKKα overexpression enhanced the expression of SREBPs and of their target genes, whereas IKKα silencing had the opposite effect. Moreover, and similarly to IKKα silencing, depletion of SREBP1 and SREBP2 impaired HCV particle production, probably owing to decreased lipid droplet formation.

Thus, in the context of HCV infection, IKKα has a pro-viral role, facilitating viral particle assembly by promoting lipid droplet formation. Further work is now needed to determine whether chemical inhibitors of IKKα could be used as HCV antivirals.

Rachel David

ORIGINAL RESEARCH PAPER Li, Q. *et al.* Hepatitis C virus infection activates an innate pathway involving IKK-α in lipogenesis and viral assembly. *Nature Med.* 26 May 2013 (doi:10.1038/nm.3190)