Hepatitis C virus and Cytomegalovirus use peroxisomes as signaling platforms for evasion of the cellular immune response

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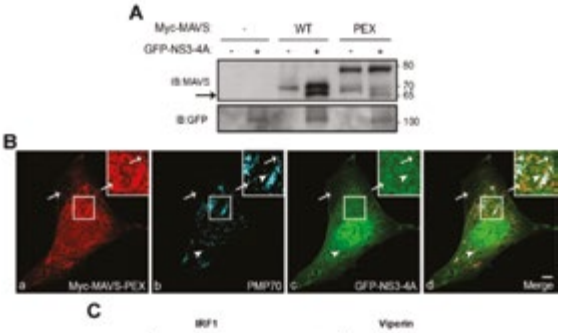
The antiviral defense in mammalian cells can be triggered upon recognition of viral genetic material by soluble proteins such as RIG-I (retinoic acid inducible gene-I), which interacts with MAVS (mitochondrial antiviral signaling adaptor) at peroxisomes and mitochondria. This initiates a signaling cascade that culminates with the production of interferons and ISGs (interferon stimulated genes), preventing important steps in viral propagation. However, in a constant adaptation to their host cells, viruses have developed several different strategies to evade antiviral defenses.

We have recently demonstrated that the hepatitis C virus (HCV) protein NS3-4A is able to specifically cleave the peroxisomal MAVS, leading to the production of a smaller fragment (Fig. 1 A) that is relocated to the cytosol (Fig. 1 B). This cleavage leads to an inhibition of the production of ISGs of such as IRF1 and viperin (Fig. 1 C), consequently disrupting the cellular antiviral defense.

Our results have also recently revealed that the human cytomegalovirus (HCMV) protein vMIA (viral mitochondria-localized inhibitor of apoptosis), localizes at peroxisomes (Fig 2 A, B), where it interacts with MAVS (Fig. 2 C) and specifically inhibits the peroxisomal MAVS-dependent pathway (Fig. 2 D).

Our studies demonstrate that both viruses have developed mechanisms by which they specifically interfere with peroxisomes in order to evade the immune response. Components of this signaling machinery may, hence, prove to be valuable targets for the development of broad-spectrum antiviral combat strategies by the pharmaceutical industry.



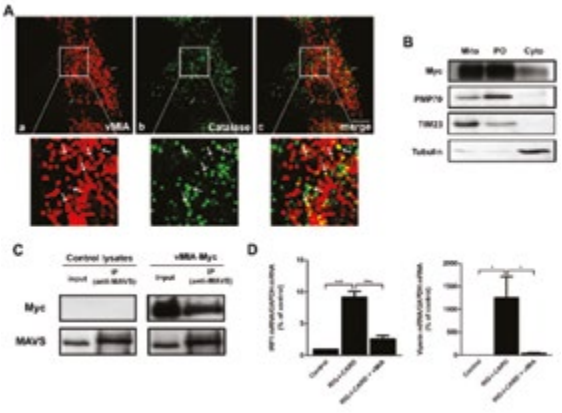


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FIGURE 1
Peroxisomal MAVS cleavage by HCV NS3-4A evaluated by Western blot (A) and immunofluorescence confocal microscopy analyses (B). Inhibition of the peroxisome-dependent MAVS pathway by NS3-4A in cells that contain MAVS solely at peroxisomes, evaluated by RT-qPCR (C).

FIGURE 2
Peroxisomal localization of vMIA in HFF cells infected with HCMV demonstrated by immunofluorescence and confocal microscopy analyses (A) and cellular fractionation (B). Interaction between vMIA and peroxisomal MAVS demonstrated by co-immunoprecipitation analysis (C). Inhibition of the peroxisomal dependent antiviral signaling by vMIA in cells that contain MAVS solely at peroxisomes, demonstrated by RT-qPCR analysis (D).