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Abstract

Peroxisomes as Platforms for Cytomegalovirus' Evasion from Cellular Antiviral Signaling †

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Abstract: Peroxisomes, in concert with mitochondria, have been established as platforms for the establishment of a rapid and stable antiviral immune response, due to the presence of the mitochondrial antiviral signaling protein (MAVS) at their membranes. Upon intracellular recognition of viral RNA, retinoic acid inducible gene-I (RIG-I)-like proteins interact with MAVS, inducing its oligomerization and the establishment of a signaling cascade that culminates with the production of direct antiviral effectors, preventing important steps in viral propagation. We and others have demonstrated that different viruses have developed specific mechanisms to counteract peroxisome-dependent antiviral signaling. We have shown that the human cytomegalovirus (HCMV) protein vMIA hijacks the peroxisome transport machinery to travel to the organelle, interact with MAVS, and inhibit the immune response. Here, we further unravel the mechanisms by which HCMV is able to evade peroxisome-dependent antiviral signaling. We demonstrate that vMIA localizes at the peroxisomes in a complex with MAVS and the stimulator of interferon genes (STING) protein. Furthermore, vMia interacts with mitochondrial fission factor (MFF) at the peroxisomal membrane, which we show to be essential for vMia-dependent inhibition of the antiviral immune response. Importantly, we demonstrate that vMIA's interaction with MAVS impedes its oligomerization and the consequent activation of the downstream signaling cascade. Interestingly, our results underline important differences between vMIA's mechanisms of action at the peroxisomes and the mitochondria. Our results unravel novel mechanisms involving the interplay between the HCMV and peroxisomes that may ultimately contribute to the discovery of novel targets for antiviral combat.

Keywords: peroxisomes; human cytomegalovirus; vMIA; antiviral signaling; MAVS