Life science, Cell biology

MAVS is energized by Mff which senses mitochondrial metabolism via AMPK for acute antiviral immunity

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Abstract

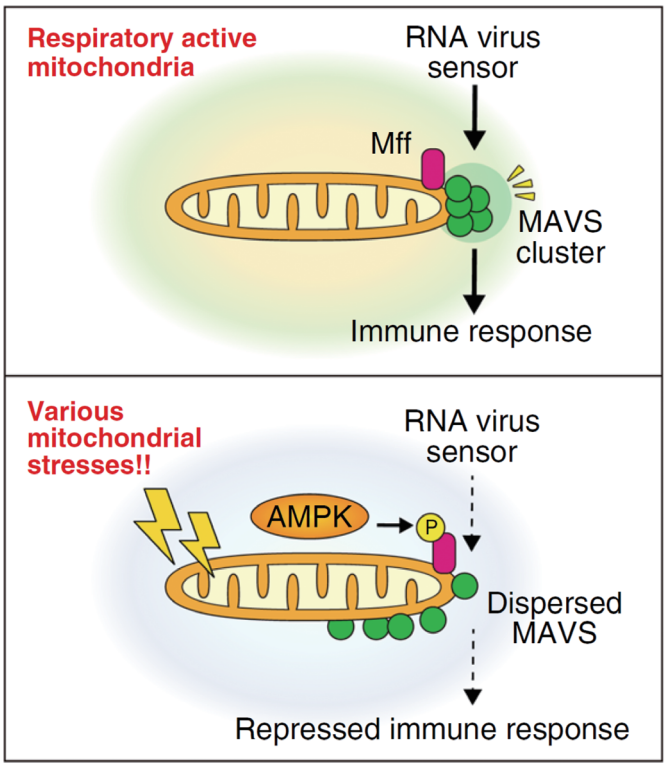
Mitochondria are multifunctional organelles that produce energy and are critical for various signaling pathways. Mitochondrial antiviral signaling (MAVS) is a mitochondrial outer membrane protein essential for the anti-RNA viral immune response, which is regulated by mitochondrial dynamics and energetics; however, the molecular link between mitochondrial metabolism and immunity is unclear. Here we show in cultured mammalian cells that MAVS is activated by mitochondrial fission factor (Mff), which senses mitochondrial energy status. Mff mediates the formation of active MAVS clusters on mitochondria, independent of mitochondrial fission and dynamin-related protein 1. Under mitochondrial dysfunction, Mff is phosphorylated by the cellular energy sensor AMP-activated kinase (AMPK), leading to the disorganization of MAVS clusters and repression of the acute antiviral response. Mff also contributes to immune tolerance during chronic infection by disrupting the mitochondrial MAVS clusters. Taken together, Mff has a critical function in MAVS-mediated innate immunity, by sensing mitochondrial energy metabolism via AMPK signaling.

Background & Results

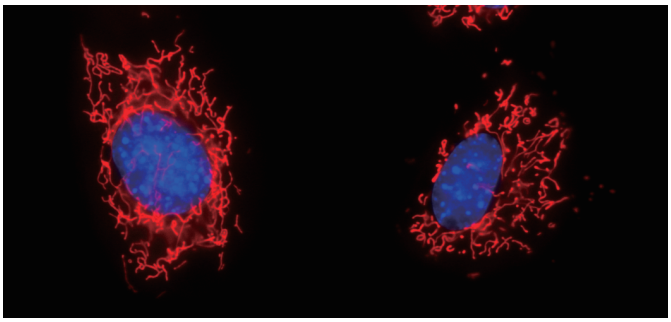
Mitochondria are believed to be derived from endosymbiosis of bacteria; however, mitochondria also act as a platform of innate immune signaling, through mitochondrial antiviral signaling (MAVS) protein on mitochondrial outer membrane. This antiviral platform is not static because mitochondria are dynamic organelles, move in cytoplasm and frequently divide and fuse each other. However, it remains largely unknown how the mitochondrial dynamics serves to defend infected pathogens.

Significance of the research and Future perspective

To investigate the role of mitochondria in MAVS-mediated innate immunity, we focused on Mff, which is also located on mitochondrial outer membrane and regulates mitochondrial fission under cellular signaling. Here we found that Mff plays critical roles in formation of membrane subdomain localizing active MAVS. Under nutrition starvation or defected in mitochondrial metabolism, Mff is phosphorylated at Ser 146 by ATP sensor AMPK, which repressed the antiviral signaling. This report reveals a novel aspect of mitochondrial function on cellular signaling, in which mitochondrial fission factor and innate immunity are coupled.



Working hypothesis for how mitochondrial dysfunction leads to the suppression of the antiviral response by the AMPK–Mff axis.



Mitochondrial network structures in mouse embryonic fibroblasts (MEFs). Mitochondria are stained as red and nucleus are stained as blue.

Patent
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