MS54.O04

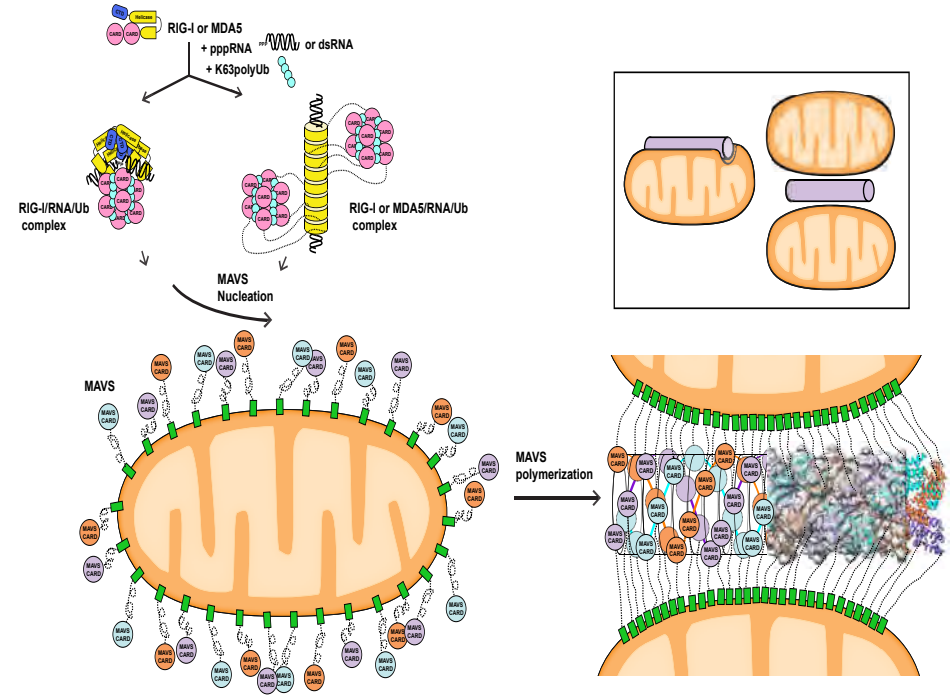
Structural basis for filament formation of MAVS on mitochondria by cryoEM

Q. Jiang[1], X. He[3], H. Zheng[1], L. Huang[1], F. Hou[4], Z. Yu[5], M. de la Cruz[5], B. Borkowski[1], X. Zhang[3], Z. Chen[6], Q. Jiang[1]

[1]UT Southwestern Medical Center, Department of Cell Biology, Dallas, TX, USA, [2]UT Southwestern Medical Center, Department of Molecular Biology, Dallas, TX, USA, [3]UT Southwestern Medical Center, Department of Pharmacology, Dallas, TX, USA, [4]Shanghai Institutes for Biological Sciences, CAS, State Key Lab of Cell Biology, Shanghai, China, [5]CryoEM shared resources, HHMI, Ashburn, US, [6]UT Southwestern Medical Center, Department of Molecular Biology, Dallas, HHMI, TX, USA

Mitochondrial anti-viral signaling (MAVS) protein is required for innate immune responses against RNA viruses. In virus-infected cells MAVS forms prion-like aggregates to activate antiviral signaling cascades, but the underlying structural mechanism is unknown. Here we report cryo-electron microscopic structures of the helical filaments formed by both the N-terminal caspase activation and recruitment domain (CARD) of MAVS and a truncated MAVS lacking part of the proline-rich region and the C-terminal transmembrane domain. Iterative helical real space refinement was used to analyze cryoEM images of the filaments. The CARD filament structure was resolved at 9.6 angstrom with rod-like densities fitting with four alpha helices of the domain. That of the truncated MAVS was resolved at 16.4 angstroms, showing the arrangement of the middle segment of MAVS at the periphery of the CARD filament. Both structures are left-handed three-stranded helical filaments, revealing specific interfaces between individual CARD subunits that are dictated by electrostatic interactions between neighboring strands and hydrophobic interactions within each strand. Point mutations at multiple locations of these two interfaces impaired filament formation and antiviral signaling. Super-resolution imaging of virus-infected cells revealed rod-shaped MAVS clusters on mitochondria. These results elucidate the structural mechanism of MAVS polymerization, and explain how an α-helical domain uses distinct chemical interactions to form self-perpetuating filaments.

Figure 6



Keywords: single particle cryoEM, viral RNA sensing, prion-like MAVS filaments