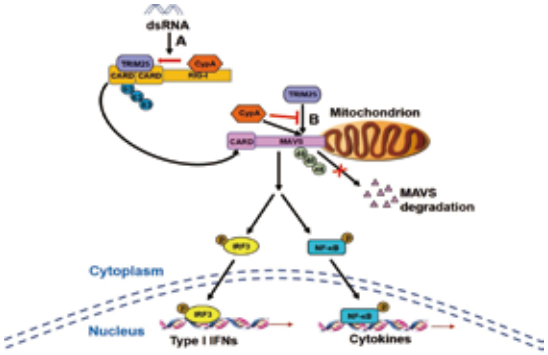
Cyclophilin A-regulated Ubiquitination Found Critical for RIG-I-mediated Antiviral Immune Responses

Cyclophilin A (CypA, encoded by PPIA) is a peptidyl-prolyl cis/trans isomerase (PPIase) that is expressed ubiquitously in all type of cells. CypA is the major cellular target for the immunosuppressive drug cyclosporin A (CsA) and is involved in protein folding, cell signaling, inflammation, and tumorigenesis. Recent work suggests that it also plays a role in regulating virus replication.

Prof. LIU Wenjun's group at the Institute of Microbiology, Chinese Academy of Sciences (IMCAS) has been working on the function of CypA in regulating virus replication for many years. In their recent exploration, they found that CypA-overexpressing transgenic mice exhibited resistance to influenza A virus infection. Moreover, they observed that CypA interacted with influenza A virus M1 protein and inhibited virus replication by accelerating ubiquitin-proteasome degradation of the M1 protein, indicating that CypA can interact directly with viral protein to regulate virus replication. Several lines of evidence indicate that CypA can also regulate virus replication through modulating host immune responses. However, the molecular mechanism regulating the antiviral immune responses of CypA is rarely understood.

The receptor RIG-I (retinoic acid-inducible gene 1) can detect viral RNA and interact with MAVS to stimulate antiviral immune responses, leading to the production of type I interferons. Prof. LIU Wenjun's group reveals an essential role of CypA in boosting RIG-I-mediated antiviral immune responses by controlling the ubiquitination of RIG-I and MAVS.

Deficiency of CypA impaired RIG-I-mediated type I IFN production and promoted viral replication in human cells and mice. Upon Sendai virus infection, CypA increased the interaction between RIG-I and its E3 ubiquitin ligase TRIM25, leading to enhanced TRIM25-mediated K63-linked ubiquitination of RIG-I that facilitated recruitment of RIG-I to MAVS. In addition, CypA and TRIM25 competitively interacted with MAVS, thereby inhibiting TRIM25-induced K48-linked ubiquitination of MAVS.



CypA boosts RIG-I-mediated antiviral immune responses: A. The binding of CypA to RIG-I-C promotes the interaction between TRIM25 and RIG-I-N, leading to enhanced TRIM25-mediated K63-linked ubiquitination of RIG-I that facilitates recruitment of RIG-I to MAVS; B. CypA and TRIM25 competitively interacts with MAVS, thereby inhibiting TRIM25-induced K48-linked ubiquitination of MAVS. (Image by Prof. LIU Wenjun's group)

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