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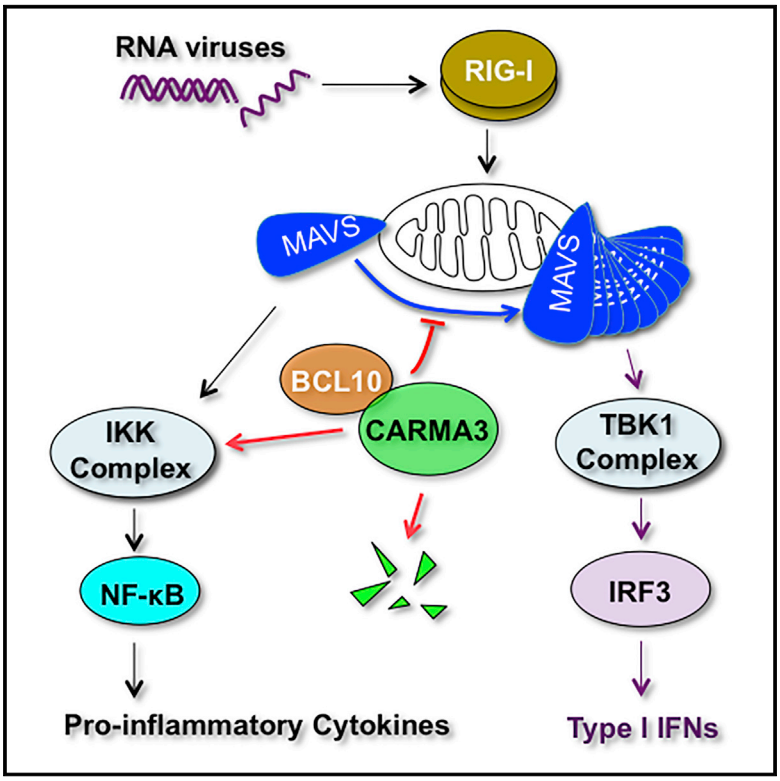
CARMA3 Is a Host Factor Regulating the Balance of Inflammatory and Antiviral Responses against Viral Infection

Graphical Abstract



Highlights

- Deficiency of CARMA3 results in the host resistance to RNA viral infection
- CARMA3 positively regulates RIG-I/MAVS-mediated NF-κB activation
- CARMA3 negatively regulates RIG-I/MAVS-mediated TBK1/IRF3 activation
- CARMA3 negatively suppresses MAVS oligomerization in mitochondran

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In Brief

Jiang et al. reveal that *CARMA3*, a gene located in a host genomic locus that contributes to the host's susceptibility to RNA respiratory virus infection, is a key molecule that controls the balance of pro-inflammatory and antiviral responses, through positively regulating NF-κB activation but negatively regulating IRF3 activation.

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CARMA3 Is a Host Factor Regulating the Balance of Inflammatory and Antiviral Responses against Viral Infection

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SUMMARY

Host response to RNA virus infection is sensed by RNA sensors such as RIG-I, which induces MAVS-mediated NF-κB and IRF3 activation to promote inflammatory and antiviral responses, respectively. Here, we have found that CARMA3, a scaffold protein previously shown to mediate NF-κB activation induced by GPCR and EGFR, positively regulates MAVS-induced NF-κB activation. However, our data suggest that CARMA3 sequesters MAVS from forming high-molecular-weight aggregates, thereby suppressing TBK1/IRF3 activation. Interestingly, following NF-κB activation upon virus infection, CARMA3 is targeted for proteasome-dependent degradation, which releases MAVS to activate IRF3. When challenged with vesicular stomatitis virus or influenza A virus, CARMA3-deficient mice showed reduced disease symptoms compared to those of wild-type mice as a result of less inflammation and a stronger ability to clear infected virus. Altogether, our results reveal the role of CARMA3 in regulating the balance of host antiviral and pro-inflammatory responses against RNA virus infection.

INTRODUCTION

The innate immune system is the first line of host defense against infection, which is essential for initial detection and recognition of pathogens, activation of acute anti-microbial responses, and subsequent activation of adaptive immunity. This system utilizes pattern recognition receptors such as Toll-like receptors (TLRs) on the cell surface and cytosolic retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs) to detect the invading pathogen (Baum and García-Sastre, 2011; Janeway, 2013; Jiang et al., 2011a). The RLR family of proteins is crucial for detecting viral RNA in cytosol. It is composed of RIG-I, melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). RIG-I senses 5′-triphosphate RNA as well as short (<2-kb) double-stranded RNA (dsRNA) and is essential for innate immunity to many single-stranded RNA (ssRNA) viruses, including influenza A virus (IAV), Sendai virus (SeV), respiratory syncytial virus (RSV), vesicular stomatitis virus (VSV), etc. In contrast, MDA5 recognizes longer dsRNA (>2 kb) and protects the host from infection of encephalomyocarditis virus (EMCV), Theiler's virus, mengovirus, murine norovirus, and murine hepatitis virus (Kato et al., 2006; McCartney et al., 2008; Roth-Cross et al., 2008).

Without stimulation, RIG-I is in the closed conformation with the N-terminal CARD domains bound to the central helicase domain. Upon binding of the CTD to viral RNA, RIG-I undergoes conformational changes, oligomerization, and exposure of the CARD domains to recruit a signaling adaptor called mitochondrial antiviral-signaling protein (MAVS). MAVS contains an N-terminal CARD domain, a proline-rich region, and a transmembrane domain (TMD) at the C terminus. The CARD domain is important for its interaction with upstream RLRs (Goubau et al., 2014; Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005). The proline-rich region is required for the recruitment of multiple E3 ligases, such as tumor necrosis factor (TNF) receptor (TNFR)-associated factors (TRAFs). The TMD domain is key for MAVS localization at the mitochondrial outer membrane. Upon activation, MAVS forms a functional prion-like structure at mitochondria and works as a platform to form a MAVS signalosome that further activates IKKα/IKKβ/NEMO signaling and TBK1/IKKε/NEMO signaling (Liu et al., 2013).

Activation of IKKα/IKKβ/NEMO triggers activation of transcription factor necrosis factor κB (NF-κB) and, thus, induction of pro-inflammatory cytokines (Liu and Gu, 2011). These cytokines are important to induce inflammatory responses and to restrict viral