Arginine monomethylation by PRMT7 controls MAVS-mediated antiviral innate immunity

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Innate immunity is the first line of defense against microbial infection. In response to RNA virus infection, mitochondrial antiviral signaling protein (MAVS) plays an important role in innate antiviral immune responses.

Arginine methylation is a Post-translational Modification (PTM) in histone and non-histone proteins that can affect numerous cellular activities. Previous studies have revealed that zebrafish protein arginine methyltransferase 7 (prmt7) negatively regulates antiviral innate immunity, linking arginine methylation to the modulation of innate immunity. However, the underlying mechanisms are still largely unknown.

In a study published in *Molecular cell*, a research group led by XIAO Wuhan from the Institute of Hydrobiology (IHB) of the Chinese Academy of Sciences demonstrated that PRMT7 negatively regulates MAVS-mediated antiviral innate immune responses both in vitro and in vivo, which shows a function of PRMT7 and PRMT7-mediated arginine monomethylation in innate immunity.

The researchers first found that monomethyl arginine (MMA) proteins were readily detected with dynamic changes in bone marrow- derived dendritic cells (BMDCs) and mouse lung fibroblast cells (MLFs) using an antibody against MMA. This suggested that MMA proteins may be

involved in RIG-I-like receptor (RLR) signaling.

By screening and mass spectrometry analysis, they identified that MAVS is monomethylated at residue Arginine 52 (R52), diminishing its interaction with RNA sensor retinoic acid inducible gene I (RIG-I) and the formation of aggregates. Co-immunoprecipitation and in-vitro methylation assays showed that PRMT7 catalyzes MAVS monomethylation at R52 and prevents association between MAVS/MAVS and MAVS/RIG-I, leading to the suppression of MAVS aggregation and subsequent activation.

The researchers next investigated the cellar function of PRMT7 by overexpressing PRMT7 in human embryonic kidney 293 (HEK293T) cells or generating $PRMT7^{-/-}$ and $MAVS^{-/-}$ cells, and found that upon virus infection, real-time polymerase chain reaction (RT-PCR), phosphorylation and dimerization assays indicated that PRMT7 negatively regulates viral RNA-triggered RLR signaling by enzymatically targeting MAVS.

Besides, the researchers investigated the effects of PRMT7 on antiviral innate immunity in vivo. Using mouse model, they found that $Prmt7^{+/-}$ mice are more resistant to vesicular stomatitis virus (VSV) infection and presented higher levels of interferon beta 1 (Ifnb1) mRNA and lower VSV-N gene mRNA levels and VSV titers in lung, spleen, and liver than $Prmt7^{+/+}$ mice in response to VSV infection.

Surprisingly, they found that PRMT7 could be automethylated and that the amount of PRMT7 protein decreased during SeV infection but not herpes simplex virus 1 (HSV-1) virus infection. They revealed that viral infection induces the proteasomal degradation of PRMT7 in a MAVS-dependent manner and MAVS recruits the smad ubiquitination regulatory factor-1 (SMURF1) to PRMT7 to catalyze the K48-linked polyubiquitination of PRMT7.

These results confirmed that the negative effect of PRMT7 on RLR signaling is mediated by MAVS monomethylation in vitro and in vivo. Combined with previously studies, the findings of this study showed that CRISPR/Cas9 techniques can be used to knock out prmt7 in grass carp to obtain anti-GCRV strains, which may benefit the aquaculture industry.

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