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ZAPS acts as a key factor of RIG-I-mediated activation of innate immune responses during influenza virus

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Abstract

Innate immune system acts as the first-line of host defense against infection by microbes to activate anti-microbial responses for elimination of invading pathogens. Recent rapid progress in studies on innate immunity has facilitated the identification of various pattern recognition receptors (PRRs), which sense pathogen-derived molecular patterns (PAMPs) and evoke robust innate immune responses through the gene induction of proinflammatory cytokines and type I interferons (IFNs). Particularly, during viral infection, virus-derived nucleic acids are mainly recognized as viral PAMPs by nucleic acid sensors. Among these, a DExD/H-box RNA helicase RIG-I, is known to be a key cytosolic RNA sensor that has an important role in triggering responses to many viruses, such as influenza A virus, measles virus, hepatitis C virus, most of which are causative agents for infectious diseases in human. Recently, our group has identified the poly(ADP-ribose) polymerase-13 (PARP-13) shorter isoform "ZAPS" as a potent stimulator of the RIG-I-mediated signaling. ZAPS interacts with RIG-I to promote its activity, leading to robust activation of IRF-3 and NF-kappaB transcription factors. We also found that ZAPS contributes to RIG-I-mediated antiviral activity during influenza virus infection. On the other hand, such innate immune signalings are often targeted by viral proteins to evade host immune system. For example, it has been reported that non-structural protein 1 (NS1) of influenza virus associates with RIG-I and inhibits its downstream signalings. However, its detailed mechanism is still unknown. In our current study, we demonstrate that RIG-I-ZAPS interaction is a targeting point of NS1 protein. Our data indicate that influenza virus expresses NS1 protein to competitively inhibit the interaction of ZAPS with RIG-I for its innate immune evasion. In addition, a study with ZAPS transgenic mice also revealed an important role of ZAPS in antiviral defense against influenza virus *in vivo*. These results may provide a therapeutic insight for the control of viral infection.