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RIG-I activation by a protein-deamidating complex consisting a viral pseudoenzyme and a cellular amidotransferase

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Herpesvirus is one of the most ubiquitous pathogens in nature. A remarkable propensity of all herpesviruses is their ability to establish life-long persistent infection, known as latency. Not surprisingly, herpesviruses have evolved diverse strategies to evade and harness cellular signaling, e.g., innate immune response. We have previously reported that gamma herpesviruses utilize the mitochondrion antiviral signaling (MAVS) adaptor and IKKβ kinase to promote viral lytic replication. Specifically, activated IKK phosphorylates viral key transcription factor (RTA) to enable viral gene expression. Additionally, IKKβ was hijacked to induce the degradation of RelA, thereby terminating NF-κB activation and preventing antiviral cytokine production. These findings highlight an intricate immune evasion strategy and suggest that gamma herpesviruses have dedicated mechanism(s) to activate the MAVS-dependent signaling cascade.

Activation of pattern recognition receptors is crucial for host innate immune defense and RIG-I is a genuine RNA sensor. We describe here a mechanism of RIG-I activation enabled by amidotransferase-mediated deamidation. To dissect herpesviral immune evasion strategy, we discovered that viral homologues of phosphoribosylformyglycinamide synthase (PFAS), although lacking intrinsic enzyme activity, recruited cellular PFAS to deamidate RIG-I. Accordingly, depletion or biochemical inhibition of PFAS impaired RIG-I deamidation. Purified PFAS and viral homologues thereof deamidate RIG-I in vitro. Glutamine-deamidation within the first CARD synergized with asparagine-deamidation within the ATPase domain to activate RIG-I. Our findings show that viral pseudo enzymes and cellular PFAS activate RIG-I via deamidation, unveiling a new means by which a pattern recognition receptor is activated by an enzyme and identifying a cellular protein deamidase.

Biography

Feng has obtained his Ph.D from University of Missouri-Kansas City and postdoctoral training from Harvard Medical School. He was a Lymphoma Leukemia Society fellow and special fellow, and is currently an American Cancer Society Scholar. He has published more than 30 papers in reputed journals and serves as an editorial member of Journal of Virology, an editor of PLoS Pathogens.

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