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Linear Ubiquitination of NEMO Negatively Regulates the Interferon Antiviral Response through Disruption of the MAVS-TRAF3 Complex

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The RIG-I/Mda5 sensors recognize viral intracellular RNA and trigger host antiviral responses. RIG-I signals through the adaptor protein MAVS, which engages various TRAF family members and results in type I interferon (IFNs) and proinflammatory cytokine production via activation of IRFs and NF-κB, respectively. Both the IRF and NF-κB pathways also require the adaptor protein NEMO. We determined that the RIG-I pathway is differentially regulated by the linear ubiquitin assembly complex (LUBAC), which consists of the E3 ligases HOIL-1L, HOIP, and the accessory protein SHARPIN. LUBAC downregulated virus-mediated IFN induction by targeting NEMO for linear ubiquitination. Linear ubiquitinated NEMO associated with TRAF3 and disrupted the MAVS-TRAF3 complex, which inhibited IFN activation while stimulating NF-κB-dependent signaling. In SHARPIN-deficient MEFs, vesicular stomatitis virus replication was decreased due to increased IFN production. Linear ubiquitination thus switches NEMO from a positive to a negative regulator of RIG-I signaling, resulting in an attenuated IFN response.

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