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Abstract

Activation and Antagonism of the OAS–RNase L Pathway †

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† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 4 June 2020

Abstract: The oligoadenylate synthetase–ribonuclease L (OAS–RNase L) system is a potent antiviral pathway that severely limits the pathogenesis of many viruses. Upon sensing dsRNA, OASs produce 2′,5′-oligoadenylates (2-5A) that activate RNase L to cleave both host and viral single-stranded RNA, thereby limiting protein production, virus replication and spread, leading to apoptotic cell death. Endogenous host dsRNA, which accumulates in the absence of adenosine deaminase acting on RNA (ADAR)1, can also activate RNase L and lead to apoptotic cell death. RNase L activation and antiviral activity during infections with several types of viruses in human and bat cells is dependent on OAS3 but independent of virus-induced interferon (IFN) and, thus, RNase L can be activated even in the presence of IFN antagonists. Differently from other human viruses examined, Zika virus is resistant to the antiviral activity of RNase L and instead utilizes RNase L to enhance its replication factories to produce more infectious virus. Some betacoronaviruses antagonize RNase L activation by expressing 2′,5′-phosphodiesterases (PDEs) that cleave 2-5A and thereby antagonize activation of RNase L. The best characterized of these PDEs is the murine coronavirus (MHV) NS2 accessory protein. Enzymatically active NS2 is required for replication in myeloid cells and in the liver. Interestingly, while wild type mice clear MHV from the liver by 7–10 days post-infection, RNase L knockout mice fail to effectively clear MHV, probably due to diminished apoptotic death of infected cells. We suggest that RNase L antiviral activity stems from direct cleavage of viral genomes and cessation of protein synthesis as well as through promoting death of infected cells, limiting the spread of virus. Importantly, OASs are pattern recognition receptors and the OAS–RNase L pathway is a primary innate response pathway to viruses, capable of early response, coming into play before IFN is induced or when the virus shuts down IFN signaling.

Keywords: murine coronavirus; oligoadenylate-ribonuclease L; interferon antagonist; phosphodiesterase; OAS3; ADAR1

Funding: The research is funded by NIH R01-AI1104887; R01-AI140442.