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Journal

DNA and Cell Biology, 41(4)

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Publication Date

2022-04-01

DOI

10.1089/dna.2022.0071

Peer reviewed

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DNA AND CELL BIOLOGY
Volume 41, Number 4, 2022
© Mary Ann Liebert, Inc.
Pp. 331–335
DOI: 10.1089/dna.2022.0071

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Analyzing Opposing Interactions Between Sphingosine 1-Phosphate Lyase and Influenza A Virus

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Sphingosine 1-phosphate lyase (SPL) is a critical component of sphingosine 1-phosphate (S1P) metabolism. SPL has been associated with several crucial cellular functions due to its role in S1P metabolism, but its role in viral infections is poorly understood. Studies show that SPL has an antiviral function against influenza A virus (IAV) by interacting with IKKε, promoting the type I interferon (IFN) innate immune response to IAV infection. However, a more recent study has revealed that IAV NS1 protein hampers this by triggering ubiquitination and subsequent degradation of SPL, which reduces the type I IFN innate immune response. In this study, we describe SPL, the type I IFN response, and known interactions between SPL and IAV.

Keywords: sphingosine-1-phosphate lyase, type I interferon, viral immune evasion, influenza A virus, virus–host interactions

Introduction

Influenza viruses cause annual seasonal influenza outbreaks (Lam *et al.*, 2019), which result in substantial hospitalizations, morbidity, and mortality worldwide (Iuliano *et al.*, 2018; Blanton *et al.*, 2019). Seasonal influenza vaccines are available and reformulated annually (Krammer *et al.*, 2018), but it is difficult to predict exactly which strain of influenza virus will infect the population due to its high rate of mutation. In addition, multiple influenza A virus (IAV) strains are resistant to contemporary antivirals (Irwin *et al.*, 2016; Hussain *et al.*, 2017). Therefore, it is critical to identify new targets to counteract IAV infection.

Sphingosine 1-phosphate (S1P) lyase (SPL) is a host enzyme in the S1P metabolic pathway that irreversibly catalyzes the cleavage of S1P into hexadecenal and phosphoethanolamine (Spiegel and Milstien, 2003). Because S1P has crucial functions in several cellular pathways, it is an important target for treating human disease. For example, sphingosine analog FTY720 is used to treat multiple sclerosis flare-ups (Brinkmann *et al.*, 2010). Furthermore, a growing body of studies indicates that many viruses regulate S1P-metabolizing enzymes to enhance viral replication or pathogenicity, suggesting that these enzymes play a crucial role during viral infections (Wolf *et al.*, 2019).

Thus, manipulation of S1P metabolizing enzymes has great potential for the development of new therapeutics against several viral diseases (Xia *et al.*, 2018; Studstill *et al.*, 2020). However, the involvement of SPL in viral infection has only recently begun to be characterized. It has been shown that SPL has antiviral activity against IAV (Seo *et al.*, 2010; Vijayan *et al.*, 2017). However, a recently published study shows that IAV infection ultimately counteracts this (Wolf *et al.*, 2021). This review highlights SPL, the retinoic acid-inducible gene I (RIG-I)-mediated type I interferon (IFN) response, and IAV–SPL interactions.

S1P Lyase

SPL is the final enzyme of the common degradative pathway through which all sphingolipids are catabolized (Gault *et al.*, 2010; Saba, 2019). This highly conserved enzyme serves as the gatekeeper of sphingolipid metabolism, guarding its only exit point.

SPL catalyzes the pyridoxal 5′-phosphate cofactor-assisted cleavage of S1P and other sphingoid base phosphates at the C2-3 carbon–carbon bond. The reaction irreversibly eliminates the phosphorylated sphingoid base, producing a long-chain aldehyde (hexadecenal, in the case of S1P) and ethanolamine phosphate (Bourquin *et al.*, 2010). Disruption of genes encoding SPL orthologs in fruit flies, nematodes, and mice cause developmental and reproductive defects, neurological impairment, and early lethality (Herr *et al.*, 2003; Samuelson *et al.*, 2007; Schmahl *et al.*, 2007; Bektas *et al.*, 2010; Atkinson *et al.*, 2017).

In 2017, the discovery of SPL insufficiency syndrome (SPLIS), a devastating inborn error of metabolism manifesting

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as immunological, renal, neurological, skin and endocrine defects, revealed that SPL function is also essential for human life (Janecke *et al.*, 2017; Lovric *et al.*, 2017; Prasad *et al.*, 2017). In addition to the importance of SPL in intrinsic organ function as revealed by SPLIS, recent studies have shown that SPL contributes to host–pathogen interactions. For example, some bacteria produce and secrete SPL enzymes that serve as virulence factors, reducing intracellular S1P and enabling the intracellular survival of the microbe (Degtyar *et al.*, 2009; Custódio *et al.*, 2016; Rolando *et al.*, 2016).

In contrast, host SPL can regulate the immune response to viral infection, as we will describe hereunder. Some consequences of SPL inactivation (such as SPLIS nephropathy) can likely be attributed to increased intracellular S1P and/or aberrant S1P receptor activation. Accumulation of cytotoxic ceramides has been implicated in other phenotypes, such as the thymic involution observed in SPL knockout mice (Weber *et al.*, 2009). Alternatively, hippocampal neuron defects found in brain-specific SPL knockout mice have been attributed to the depletion of SPL reaction products—which also have important roles in autophagy, apoptosis, and DNA modification (Mitroi *et al.*, 2016, 2017).

Influenza Viral Regulation of the RIG-I-Mediated Type I IFN Response

The type I IFN innate immune response is among the first lines of defense against viral infections (Fig. 1) (Seo and Hahm, 2010; Hoffmann *et al.*, 2015). However, despite being well-equipped to counteract viral pathogens, the innate immune response is not always successful in preventing viral infections. IAV has adapted to overcome the type I IFN innate immune response and facilitate its replication, which must occur for robust viral replication (Muñoz-Moreno *et al.*, 2020). IAV polymerase basic protein (PB) 2 (PB2) and PB1-F2 proteins inhibit the induction of type I IFNs by binding to mitochondrial

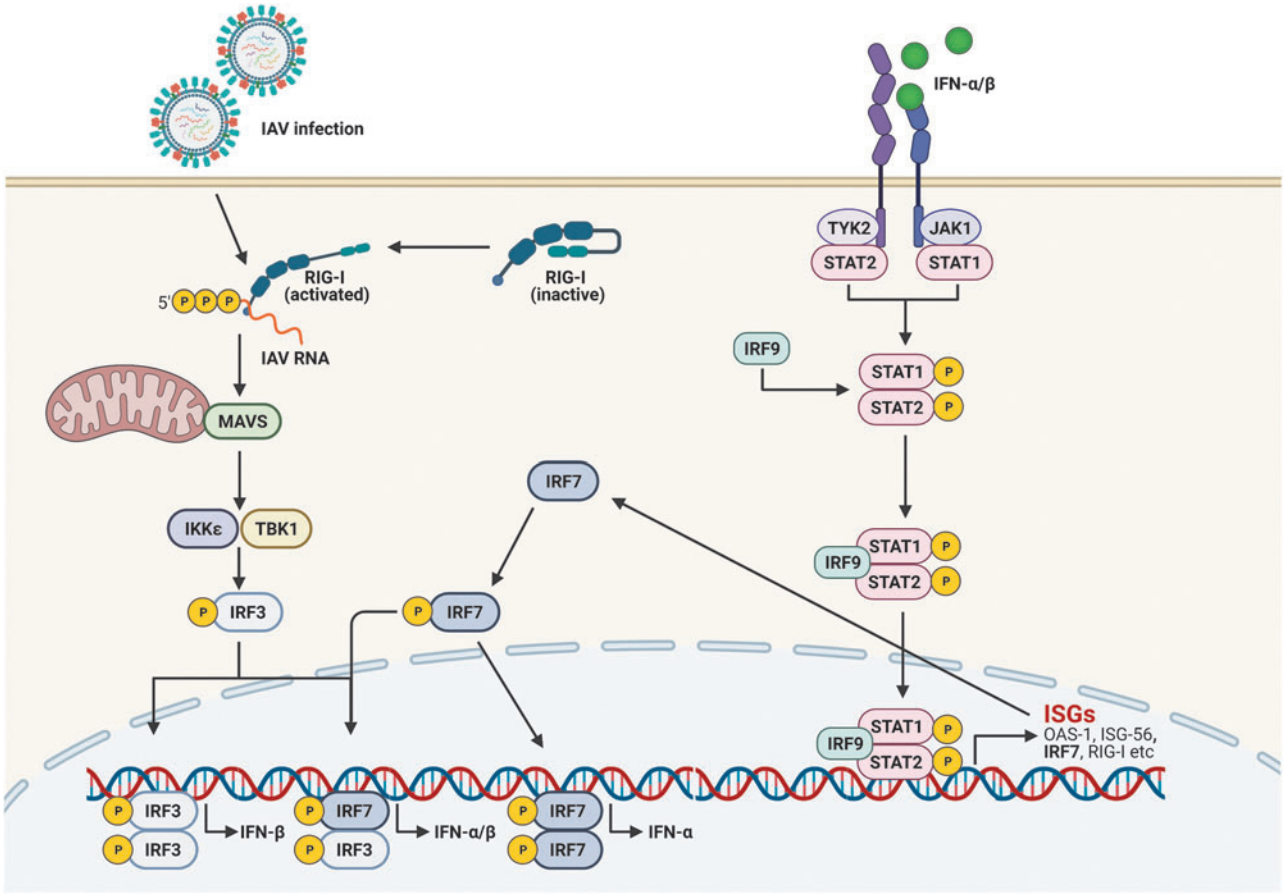

FIG. 1. The RIG-I-mediated type I IFN response to IAV. After IAV infection, RIG-I initiates an antiviral response by recognizing and binding IAV 5′-triphosphate RNA. RIG-I then activates the downstream adaptor protein MAVS. MAVS serves as a scaffold protein to recruit downstream kinases TBK1 and IKKε. These two kinases then phosphorylate IRF3 and later IRF7, both of which are transcription factors that can lead to IFN production. IRF3 and IRF7 either homodimerize or heterodimerize and translocate to the nucleus, where the dimer complexes with coactivators and binds to its target DNA sequence in type I IFN genes, leading to the production of IFN-β and IFN-α. The secreted type I IFNs act by binding to the cognate IFNAR, which initiates the JAK/STAT pathway that leads to induction of ISGs. JAK1 and TYK2 phosphorylate STAT1/STAT2, which then complexes with IRF9, forming the ISGF3 complex. The ISGF3 complex then localizes to the nucleus where it induces the expression of ISGs. RIG-I, retinoic acid-inducible gene I; MAVS, mitochondrial antiviral signaling protein; TBK1, TANK-binding kinase I; IKKε, inhibitor of nuclear factor kappa-B kinase subunit epsilon; IRF, interferon regulatory factor; IFN, interferon; IFNAR, interferon alpha and beta receptor subunit; JAK, janus kinase; TYK, non-receptor tyrosine-protein kinase; STAT, signal transducer and activator of transcription; ISGs, IFN-stimulated genes; ISGF, ISG factor.

antiviral-signaling protein (MAVS), which decreases mitochondrial membrane potential (Graef *et al.*, 2010; Varga *et al.*, 2012).

IAV hemagglutinin protein (HA) induces downregulation of interferon alpha and beta receptor subunit 1 (IFNAR1), which reduces the type I IFN innate immune response (Xia *et al.*, 2016). The viral non-structural protein 1 (NS1) protein is considered to be the main antagonist of the type I IFN innate immune response during IAV infection. Influenza virus inhibits the host type I IFN response by NS1 binding to double-stranded RNA (dsRNA) (Wang *et al.*, 1999). NS1 has also been shown to outcompete oligoadenylate synthetase (OAS) for dsRNA, inhibiting OAS-1 activation (Min and Krug, 2006). In addition, NS1 binding to dsRNA hinders dsRNA-activated protein kinase (PKR) activation (Bergmann *et al.*, 2000).

This induces phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2-α), leading to a decrease in the rate of initiation of translation. NS1 also blocks the tripartite motif-containing protein 25 (TRIM25)-mediated K63-linked ubiquitination of the viral RNA sensor RIG-I (Gack *et al.*, 2009), which is required for optimal downstream signaling of the type I IFN response. In addition, NS1 interacts with ring finger protein 135 (RIPLET, RNF135) to prevent RIG-I ubiquitination (Rajsbaum *et al.*, 2012) and directly binds to RIG-I to prevent RIG-I-mediated induction of the type I IFN innate immune response (Mibayashi *et al.*, 2007; Jureka *et al.*, 2020).

S1P Lyase is a pro-IFN Factor

Research has revealed that SPL has anti-IAV activity. Both human embryonic kidney 293 cells and human lung epithelial A549 cells transiently overexpressing SPL are more resistant to cell death during IAV infection, which seems to be due to overexpressed SPL regulating IAV replication (Seo *et al.*, 2010). In addition, IAV replication and viral propagation substantially increase in SPL-deficient cells, confirming the antiviral function of SPL.

A later study that expanded upon these findings showed that SPL increases type I IFN production during IAV infection or cellular recognition of influenza viral RNAs (Vijayan *et al.*, 2017). TANK-binding kinase 1 (TBK1) and inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKKε) are known to be crucial for the production of type I IFNs. Upon testing, it was determined that SPL interacts with IKKε but not with TBK1. Interestingly, the pro-IFN function of SPL is independent of the ability of SPL to catalyze S1P cleavage, and it appears to be mediated through interaction with IKKε. Furthermore, SPL increases IKKε activation but not TBK1 activation, and IKKε is critical for the anti-influenza activity of SPL.

S1P Lyase is Targeted by IAV NS1

Further characterization of SPL antiviral activity revealed that IAV infection decreases SPL levels in both A549 cells and primary human tracheal epithelial cells (Wolf *et al.*, 2021). This decrease notably occurs during infection with IAV H1N1 and H3N2 subtypes as well as with influenza B virus. However, measuring *SGPL1* mRNA showed that this decrease does not occur at the mRNA level, revealing that SPL decreases post-transcriptionally. Denatured immunoprecipitation analyses showed that SPL ubiquitination occurs during IAV infection.

In addition, SPL protein levels did not change significantly upon stimulation of the type I IFN innate immune response with either recombinant IFN-α or with IAV RNA, confirming that this is not due to the innate immune response. Upon testing various influenza viral proteins, it was observed that

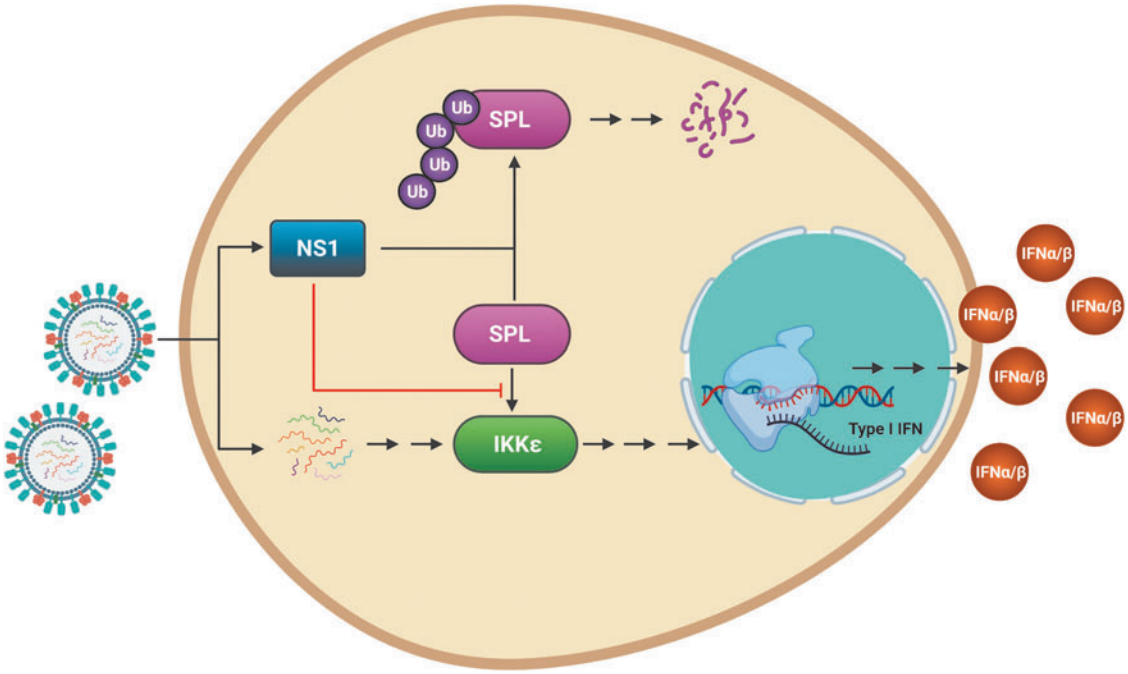

FIG. 2. IAV NS1 induces degradation of sphingosine 1-phosphate lyase to dampen the host innate immune response. SPL functions as a positive regulator of IKKε to enable the induction of a robust type I IFN response. However, IAV NS1 protein dampens the type I IFN response by inducing ubiquitination and subsequent degradation of SPL, allowing IAV to replicate more efficiently. IAV, influenza A virus; SPL, sphingosine 1-phosphate lyase.

NS1 expression is key for SPL ubiquitination and degradation. SPL undergoes both proteasomal and lysosomal degradation during NS1 expression. Furthermore, whereas wild-type IAV infection leads to ubiquitination and degradation of SPL, infection with NS1-deficient IAV does not.

To conclude the study and tie it back to previously published results regarding the immune function of SPL, the effect of NS1 on the SPL-mediated type I IFN innate immune response was tested. Phosphorylated IKKε levels increase during overexpression of both IKKε and SPL, matching the results from the previous study. However, this increase diminishes when NS1 is additionally expressed. A similar trend occurs upon measuring mRNA levels of *IFN*-α, *IFN*-β, and IFN-stimulated gene *OAS-1*. During overexpression of both IKKε and SPL, *IFN*-α, *IFN*-β, and *OAS-1* mRNA levels increase. However, the additional expression of NS1 eliminates the observed increase. This study ultimately revealed a novel mechanism of NS1 subverting the RIG-I-mediated type I IFN innate immune response, which is summarized in Figure 2.

Perspective

Viral infection is an intricate web of interactions where the host attempts to eliminate the virus, whereas the virus must circumvent host defenses to further its replication. Although SPL is known to have many functions in the host, only recently was its antiviral function in the type I IFN innate immune response discovered. A more recently published study, which is described in this review (Wolf *et al.*, 2021), demonstrates that IAV NS1 induces the ubiquitination and subsequent degradation of host SPL.

This downregulation allows IAV to subvert the SPL-mediated type I IFN innate immune response to IAV infection. Overall, the study sheds light on the intricate interactions between influenza virus and the host immune defense and confirms the critical role of SPL in the RIG-I-mediated innate immune response. Further clarifying the mechanism of how SPL promotes the antiviral response to IAV infection and how IAV NS1 targets SPL for degradation would increase our understanding of host–pathogen interactions and could yield potential new therapeutic targets.

Since SPL functions as a pro-IFN factor, SPL may be targeted by many other pathogenic viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Levels of sphingolipids such as sphingosine and S1P are altered in coronavirus disease 2019 (COVID-19) patients, and COVID-19 severity can be predicted by observing levels of these sphingolipids (Janneh *et al.*, 2021; Marfia *et al.*, 2021). However, it remains unknown whether SARS-CoV-2 regulates the sphingolipid pathway to effectively propagate within the host, which warrants further investigation. SPL may also have antiviral effects against viruses such as SARS-CoV-2. Overall, virus–SPL interactions are a promising avenue of research that could ultimately lead to the development of novel therapeutics to treat viral infection.

Disclosure Statement

No competing financial interests exist.

Funding Information

This study was supported by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID) grants R01AI162631 (B.H.) and R01AI153076 (B.H.), the NIH/NIDDK grant R01DK115669 (J.D.S.), and the Swim Across America Foundation (J.D.S.). BioRender .com was used to make Figures 1 and 2.

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Received for publication January 27, 2022; accepted January 27, 2022.