



RESEARCH HIGHLIGHT

Antiviral immunity: a link to bile acids

Jing Wang^{1,2}, Richard A. Flavell^{2,3,4} and Hua-Bing Li^{1,2}*Cell Research* (2019) 29:177–178; <https://doi.org/10.1038/s41422-019-0148-5>

A recent study in *Cell Research* by Hu et al. describes a novel function of intracellular bile acids (BAs), a class of cholesterol-derived metabolites, which activate several key innate antiviral signaling components through the TGR5- β -arrestin-SRC pathway to potentiate antiviral immunity. This finding adds a new metabolic regulatory dimension of innate antiviral response and provides a new antiviral strategy by supplementing BAs.

The host innate immune system initiates antiviral responses by sensing virus-derived DNAs or RNAs through a class of pattern recognition receptors (PRRs). Upon recognition of viral nucleic acids, PRRs trigger the production of type I interferons (IFNs), chemokines and proinflammatory cytokines, which promote the production of antiviral proteins and activation of adaptive immune responses.¹ In detail, viral RNA is detected by RNA sensors such as RIG-I and MDA5. Then the sensor moves to mitochondria and interacts with the mitochondrial antiviral signaling protein (VISA),² which in turn promotes VISA to form a prion-like protein complex for TRAF engaging. These processes finally transmit signals to TBK1-IRF3 and IKK α / β -NF- κ B pathways. For DNA viruses, the host recognizes foreign DNA by cyclic GMP-AMP (cGAMP) synthase (cGAS) to form liquid-like droplets, in which cGAS is activated and catalyzes the efficient production of the second messenger molecule, cGAMP. cGAMP transduces the signal to the ER-localized adaptor protein STING, which activates the downstream kinases TBK1 and IRF3 to produce type I IFNs.^{3,4}

In recent years, inter-regulation of cellular metabolism and immune response has been gradually appreciated. Bile acids (BAs), known as the amphipathic primary end-products of cholesterol metabolism, aid in digestion as well as participate in signal transduction in several hepatic and enteric pathways. They are mainly synthesized by hepatocytes and further metabolized by microbes in the gut. BAs act as signaling molecules mainly through activation of receptors, such as nuclear farnesoid X receptor (FXR) and G protein-coupled receptor (GPCR) TGR5.⁵ However, the functions of intracellular BAs in immune responses are largely unknown. In a recent paper published in *Cell Research*, Shu and colleagues discovered a previously unknown mechanism by which intracellular BAs facilitate the innate antiviral responses.⁶

Shu and colleagues began by examining the expression of BA transporter and rate-limiting biosynthesis enzymes after HSV-1 or SeV infection. They found that both viruses specifically promoted the transcription of those enzymes. Moreover, it was the immediate-early NF- κ B activation following infection of SeV and HSV-1 that promoted the expression of BA rate-limiting biosynthesis enzymes and transporter. Within cells, the accumulation of intracellular BAs post virus infection was also observed. These

results for the first time reveal that viral infection reprograms intracellular BA metabolism.

Based on the rapid accumulation of BAs in cells after virus infection, Shu and colleagues proceeded to elucidate the function of BAs in innate antiviral immunity. Remarkably, BAs enhanced viral-induced innate immune responses. Given the link between BA, TGR5 and FXR,^{5,7} the authors sought to determine the downstream responses of BAs and found that TGR5 but not FXR functions in the BA-triggered response. Since G proteins and β -arrestins are two effector proteins downstream of TGR5, the authors further verified that β -arrestin 1/2 modulate the antiviral immune response. It is previously reported that GPCR-related kinases (GRKs) facilitate the activation of GPCR by recruiting β -arrestins. GRK2 and GRK6 promote the phosphorylation of β -arrestin and then recruit SRC kinase to the GPCR/ β -arrestin complex.⁸ Consistently, the authors found that TGR5-GRK- β -arrestin mediated SRC activation and thereafter promoted the antiviral response. Taken together, BAs facilitate innate antiviral response via TGR5-GRK- β -arrestin-SRC activation.

The Src family kinases, a class of non-receptor tyrosine kinases, have been well established to regulate diverse arrays of cellular responses, including immune responses, integrin signaling, motility, and carcinogenesis. Herein, SRC interacted with RIG-I (Y9, Y92, Y95, Y130, Y140), VISA (6Y), MITA (Y245), TBK1 (Y179), IRF3 (Y107) and mediated their phosphorylation that is important for their activation. This is consistent with previous studies revealing SRC function in RIG-I- and TBK1-mediated antiviral signaling pathways.^{9,10} Furthermore, they validated the importance of the BA-TGR5 signaling pathway in antiviral response in *in vivo* mouse infection model; deletion of TGR5 led to less serum IFNs, higher viral titers, lower survival rates upon viral infection, while supplementing CDCA of BA to wild-type mice, but not TGR5 mutant mice, could greatly potentiate the innate antiviral immune response.

A recent study suggested that other members of Src family kinases, Lck, Hck and Fgr phosphorylated TBK1 at Tyr354/394 and prevented TBK1 dimerization and activation, which restrained innate antiviral responses.¹¹ This indicates the possibility that phosphorylation at different sites of signal adaptor by SRC could mediate converse antiviral immune responses. Besides, several questions remain to be elucidated. Hu et al. have shown that intracellular accumulation of BAs was triggered by immediate-early NF- κ B activation. But how is the early NF- κ B activation initiated? Would other processes other than viral infection that induce NF- κ B activation also result in BA accumulation and subsequent BA-TGR5 signaling pathway activation? Investigation into how BA accumulation and the downstream signaling

¹Shanghai Institute of Immunology, Key Laboratory of Cell Differentiation and Apoptosis of Ministry of Education of China, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ²Yale Center for ImmunoMetabolism, Shanghai Jiao Tong University School of Medicine, 200025 Shanghai, China; ³Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520-8055, USA and ⁴Howard Hughes Medical Institute, Yale University, New Haven, CT 06520-8055, USA
Correspondence: Richard A. Flavell (richard.flavell@yale.edu) or Hua-Bing Li (huabing.li@shsmu.edu.cn)

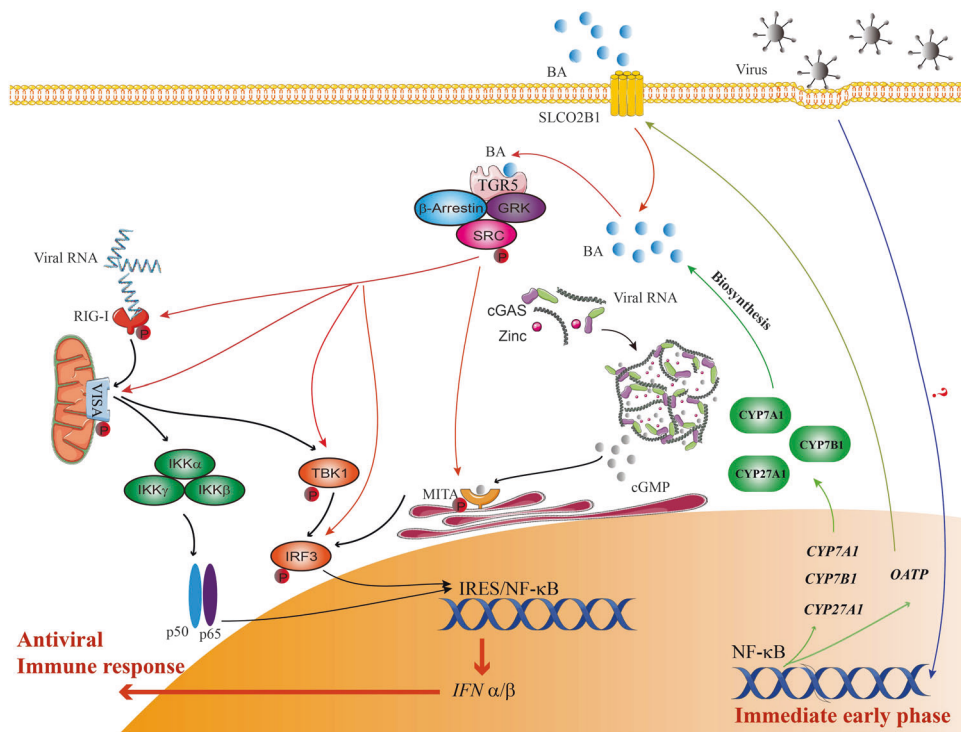


Fig. 1 BA-TGR5-GRK-β-arrestin-SRC axis promotes antiviral immune response. Immediate-early activation of NF-κB induced by virus infection promotes intracellular accumulation of BAs. BAs then activate the TGR5-GRK-β-arrestin-SRC signaling and facilitate activation of multiple innate antiviral signaling components, which finally enhance antiviral immune responses

pathway are regulated would be of interest in future studies. Furthermore, would the BA-TGR5-GRK-β-arrestin-SRC pathway modulate the development of autoimmune response and cancer? These findings would enable the exploration of BA-TGR5 axis in diverse biological processes. In addition, are other forms of metabolites also involved in immune signaling pathways and various immune responses?

The current study by Hu et al. sheds new light on the cross-talk between cellular metabolism and innate immune response post viral infection. Intracellular BA metabolism reprogramming facilitates the antiviral innate immune response via the TGR5-β-arrestin-SRC pathway (Fig. 1). Furthermore, the antiviral response could be enhanced by injection of primary BA CDCA. This study therefore highlights the exciting prospect that utilizing BAs might lead to new treatments for a wide range of virus infection.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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