

Special Issue: “Innate Immune Sensing of Viruses and Viral Evasion”

Renate König ^{1,*} and Carsten Münk ^{2,*}

¹ Host-Pathogen Interactions, Paul-Ehrlich-Institut, 63225 Langen, Germany

² Clinic for Gastroenterology, Hepatology, and Infectiology, Medical Faculty, Heinrich-Heine-University Düsseldorf, 40225 Düsseldorf, Germany

* Correspondence: reate.koenig@pei.de (R.K.); carsten.muenk@med.uni-duesseldorf.de (C.M.)

In this Special Issue, a wide variety of original and review articles provide a time-ly overview of how viruses are recognized by and evade from cellular innate immunity, which represents the first line of defense against viruses. The success of the immediate response relies on the recognition of invariant features encoded by viruses termed pathogen-associated molecular patterns (PAMPs) and by specialized sensors called pattern recognition receptors (PRRs). In the review by Singh et al., the reader is provided with a broad overview of the innate sensing of viruses by diverse PRRs. The authors discuss recent progress in the understanding of the consequences of innate sensing on the central nervous system (CNS), a tissue that can be severely damaged by infections of diverse viruses [1].

The consequence of this surveillance network and the downstream pathway activation is the secretion of cytokines and type I interferons (IFNs). Schwanke et al. provide an in-depth review on the master regulator of the type I interferon response, IRF3, and the IFN β enhancosome [2]. They present an extensive array of host or viral modulators of IRF3 activity, promoting or negatively regulating the activity upon viral stimulation. The type I IFN pathways result in the expression of interferon-stimulated genes (ISGs). A subset of ISGs possess a direct antiviral activity. These so-called restriction factors are in most cases also intrinsically expressed in some cell types without innate signaling. An example of the diversity of these factors attacking viral replication and counteraction response of the virus can be found in the review on human cytomegalovirus [3]. Large-scale screening approaches are useful tools to identify novel sensors or modulators of the innate pathways or novel antiviral ISGs expanding our knowledge on antiviral responses. Krey et al. present a detailed snapshot on such global approaches to dissect the antiviral innate immune landscape [4].

Based on the nature of their nucleic acid and entry pathways, viruses are, in general, either sensed by RNA or DNA sensors. Retroviruses, including the Human Immunodeficiency virus, are RNA viruses that reverse transcribe their RNA genome into DNA. Different aspects of RNA or DNA sensing in retroviral infections are highlighted in one review [5] and one original article [6] and a review on the distantly related endogenous retrotransposons [7]. The recognition of DNA viruses was enigmatic until the recent discovery of several DNA sensors. Poxviruses are an example of DNA viruses that express a plethora of viral antagonists that block sensing by DNA sensors, such as cGAS or DNA-PK and, interestingly, also by RNA sensors [8]. In contrast, Hepatitis B virus may evade recognition by shielding the DNA within the viral capsid, although naked HBV DNA elicits a strong immune response in primary myeloid cells mediated by cGAS/STING [9]. Hepatitis D Virus (HDV), causing the most severe form of viral hepatitis, however, activates strong IFN β / λ responses in hepatocytes. Still, counteraction strategies, e.g., hiding its viral RNAs, are discussed [10]. These publications exemplify the fact that viruses have evolved multiple ways to dampen the host IFN response by interfering, disrupting, or evading specific host regulators, both up- and downstream of IFN induction. The diverse viral escape pathways are described in the following reviews [7,8,10–

Citation: König, R.; Münk, C. Special Issue: “Innate Immune Sensing of Viruses and Viral Evasion”. *Viruses* **2021**, *13*, 567. <https://doi.org/10.3390/v13040567>

Received: 26 March 2021

Accepted: 26 March 2021

Published: 26 March 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

13] and one original article on herpes-viruses [14]. A recent discovery stems from the observation that DNA sensing by the cGAS/STING pathway can be triggered by certain RNA viruses. Zhu et al. describe an unexpected strategy of flaviviruses to antagonize this DNA sensing pathway [12]. Important players in recognizing and sensing RNA viruses are described for HDV [10] and Influenza virus [15]. Additionally, different strategies for RNA viruses to counteract innate responses are presented in original or review articles for coronaviruses [16], flaviviruses [17], orthomyxoviruses [11] and filoviruses [13]. Furthermore, unexpected pathways seem to play important roles in detecting and responding to viral infections. Eiermann et al. highlight the growing body of evidence concerning the role of stress granules in regulating antiviral innate responses and defense. They detail the crossroads of viral sensing and the stress response pathway [18]. Collectively, these reports exemplify the importance of the interplay between viruses and innate immune pathways and provide novel avenues for stimulating virus research and a perspective on possible novel targets for immune-mediated antivirals.

Acknowledgments: We would like to thank the editors, reviewers and authors for their efforts and contribution to this Special Issue of Viruses.

Funding: German Research Foundation (DFG), SPP1923 Project KO4573/1-2 to R.K. and MU 1608/9-2 to C.M. C.M. is supported by the Stiftung zur Erforschung infektiös-immunologischer Erkrankungen and the Heinz-Ansmann Foundation.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Singh, H.; Koury, J.; Kaul, M. Innate Immune Sensing of Viruses and Its Consequences for the Central Nervous System. *Viruses* **2021**, *13*, 170.
2. Schwanke, H.; Stempel, M.; Brinkmann, M. M. Of Keeping and Tipping the Balance: Host Regulation and Viral Modulation of IRF3-Dependent IFNB1 Expression. *Viruses* **2020**, *12*, 733.
3. Schilling, E. M.; Scherer, M.; Stamminger, T. Intrinsic Immune Mechanisms Restricting Human Cytomegalovirus Replication. *Viruses* **2021**, *13*, 179.
4. Krey, K.; Babnis, A. W.; Pichlmair, A. System-Based Approaches to Delineate the Antiviral Innate Immune Landscape. *Viruses* **2020**, *12*, 1196.
5. Moran, E. A.; Ross, S. R. Insights into Sensing of Murine Retroviruses. *Viruses* **2020**, *12*, 836.
6. Stunnenberg, M.; van Pul, L.; Sprockholt, J. K.; van Dort, K. A.; Gringhuis, S. I.; Geijtenbeek, T. B. H.; Kootstra, N. A. MAVS Genetic Variation Is Associated with Decreased HIV-1 Replication In Vitro and Reduced CD4(+) T Cell Infection in HIV-1-Infected Individuals. *Viruses* **2020**, *12*, 764.
7. Lagisquet, J.; Zuber, K.; Gramberg, T. Recognize Yourself—Innate Sensing of Non-LTR Retrotransposons. *Viruses* **2021**, *13*, 94.
8. Lawler, C.; Brady, G. Poxviral Targeting of Interferon Regulatory Factor Activation. *Viruses* **2020**, *12*, 1191.
9. Lauterbach-Riviere, L.; Bergez, M.; Monch, S.; Qu, B.; Riess, M.; Vondran, F. W. R.; Liese, J.; Hornung, V.; Urban, S.; Konig, R. Hepatitis B Virus DNA is a Substrate for the cGAS/STING Pathway but is not Sensed in Infected Hepatocytes. *Viruses* **2020**, *12*, 592.
10. Zhang, Z.; Urban, S. Interplay between Hepatitis D Virus and the Interferon Response. *Viruses* **2020**, *12*, 1334.
11. Malik, G.; Zhou, Y. Innate Immune Sensing of Influenza A Virus. *Viruses* **2020**, *12*, 755.
12. Zhu, T.; Fernandez-Sesma, A. Innate Immune DNA Sensing of Flaviviruses. *Viruses* **2020**, *12*, 979.
13. Wildemann, J.; Hoenen, T.; König, R. Interplay between Filoviruses and Innate Immunity. *Viruses* in preparation.
14. Mandal, P.; McCormick, A. L.; Mocarski, E. S. TNF Signaling Dictates Myeloid and Non-Myeloid Cell Crosstalk to Execute MCMV-Induced Extrinsic Apoptosis. *Viruses* **2020**, *12*, 1221.
15. Wu, W.; Zhang, W.; Tian, L.; Brown, B. R.; Walters, M. S.; Metcalf, J. P. IRF7 Is Required for the Second Phase Interferon Induction during Influenza Virus Infection in Human Lung Epithelia. *Viruses* **2020**, *12*, 377.
16. Chen, S.; Tian, J.; Li, Z.; Kang, H.; Zhang, J.; Huang, J.; Yin, H.; Hu, X.; Qu, L. Feline Infectious Peritonitis Virus Nsp5 Inhibits Type I Interferon Production by Cleaving NEMO at Multiple Sites. *Viruses* **2019**, *12*, 43.
17. Urban, C.; Welsch, H.; Heine, K.; Wust, S.; Haas, D. A.; Dachert, C.; Pandey, A.; Pichlmair, A.; Binder, M. Persistent Innate Immune Stimulation Results in IRF3-Mediated but Caspase-Independent Cytostasis. *Viruses* **2020**, *12*, 635.
18. Eiermann, N.; Haneke, K.; Sun, Z.; Stoecklin, G.; Ruggieri, A. Dance with the Devil: Stress Granules and Signaling in Antiviral Responses. *Viruses* **2020**, *12*, 984.