

## VIRAL INFECTION

## “On the bat’s back I do fly”



two recent studies provide new insights into bat virus spillover



Bats are important reservoir hosts of emerging viruses with potential major impacts on human and veterinary health. The viral diversity in bats is substantial and includes pathogens such as influenza A virus (IAV), Ebola virus and viruses related to Middle East respiratory syndrome coronavirus (MERS-CoV). Consequently, it is vital to understand the potential for zoonotic transmission of bat viruses and the underlying mechanisms of viral persistence in bats. Now, two recent studies provide new insights into bat virus spillover.

In the first study, Karakus, Thamamongood et al. identify a host cell receptor for bat IAV that is highly similar among mammals. Previous work found that the haemagglutinin glycoprotein of bat IAV does not use the canonical IAV receptor sialic acid for entry, leaving the identity of the receptor unknown. The authors used a combination of transcriptional profiling of cell lines that are permissive and non-permissive to bat IAV infection, and CRISPR–Cas9 screening to find the receptor. Both approaches independently identified the major histocompatibility complex class II (MHC II) human leukocyte

antigen DR isotype (HLA-DR) as an essential entry factor for bat IAV. Knockout of the HLA-DR  $\alpha$ -chain rendered permissive cells resistant to infection, whereas the ectopic expression of HLA-DR in non-permissive cells rendered the cells susceptible to infection. Furthermore, the authors observed that the expression of MHC II complexes from humans, mice, pigs and chickens all conferred susceptibility to infection, and MHC-II-knockout mice were resistant to bat IAV infection. These data suggest that MHC II mediates entry of bat IAV in numerous mammalian species, potentially enabling cross-species infection.

In the second study, Ahn et al. investigated the basis for the observed high viral diversity in bats, and the longevity and asymptomatic nature of many bat viral infections. The authors hypothesized that the inflammasome sensor NLR family pyrin domain containing 3 (NLRP3) has a role in causing bats to be major viral reservoirs. NLRP3 has been identified as an important mediator of inflammation in response to viral infection, including bat-borne viruses. Moreover, overactivation of NLRP3 has been linked to

a hyperinflammatory state and immunopathology without affecting viral load.

By examining primary immune cells, they observed that activation of NLRP3 is significantly dampened after stimulation with potent NLRP3 activators ATP or nigericin in bat cells compared to human or mouse cells. Moreover, NLRP3-mediated inflammation was reduced in bat cells infected with a range of zoonotic

viruses including IAV, MERS-CoV and the bat-borne virus *Pteropine orthoreovirus 3*. Remarkably, the reduction in NLRP3-mediated inflammation did not affect viral loads in bat primary immune cells compared with human and mouse cells.

On stimulation with different Toll-like receptor ligands, reduction in transcriptional priming of *NLRP3* was consistently observed in various bat immune cells compared with human and mouse cells, including peripheral blood mononuclear cells, and bone marrow-derived macrophages and dendritic cells. The authors also observed that all four NLRP3 bat isoforms had a lower induction of apoptosis-associated speck-like protein containing a CARD (ASC) speck formation (which leads to inflammatory cell death) compared with human NLRP3. Altogether, these results demonstrate that NLRP3-mediated inflammation is dampened in bats.

Overall, these results have implications for understanding why bats make such good viral hosts. The unique viral reservoir status of bats can be attributed to dampened inflammation that allows viruses to persist in the absence of disease symptoms. This feature may be a bystander effect that arose as bats adapted to the metabolic demands of flight, which can drive high levels of inflammation, necessitating an ability to throttle the inflammatory response.

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**ORIGINAL ARTICLES** Karakus, U., Thamamongood, T. et al. MHC class II proteins mediate cross-species entry of bat influenza viruses. *Nature* <https://doi.org/10.1038/s41586-019-0955-3> (2019) | Ahn, M. et al. Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. *Nat. Microbiol.* <https://doi.org/10.1038/s41564-019-0371-3> (2019)  
**FURTHER READING** Long, J. S. et al. Host and viral determinants of influenza A virus species specificity. *Nat. Rev. Microbiol.* **17**, 67–81 (2019)

