

Lessons from the host defences of bats, a unique viral reservoir

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There have been several major outbreaks of emerging viral diseases, including Hendra, Nipah, Marburg and Ebola virus diseases, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)—as well as the current pandemic of coronavirus disease 2019 (COVID-19). Notably, all of these outbreaks have been linked to suspected zoonotic transmission of bat-borne viruses. Bats—the only flying mammal—display several additional features that are unique among mammals, such as a long lifespan relative to body size, a low rate of tumorigenesis and an exceptional ability to host viruses without presenting clinical disease. Here we discuss the mechanisms that underpin the host defence system and immune tolerance of bats, and their ramifications for human health and disease. Recent studies suggest that 64 million years of adaptive evolution have shaped the host defence system of bats to balance defence and tolerance, which has resulted in a unique ability to act as an ideal reservoir host for viruses. Lessons from the effective host defence of bats would help us to better understand viral evolution and to better predict, prevent and control future viral spillovers. Studying the mechanisms of immune tolerance in bats could lead to new approaches to improving human health. We strongly believe that it is time to focus on bats in research for the benefit of both bats and humankind.

The current pandemic of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has led to more than 75,704,857 cases and caused 1,690,061 deaths (as of 21 December 2020)¹. Although the possibility of an intermediate host remains an open question, SARS-CoV-2 is believed to have an ancestral origin in bats²—with closest similarity to the bat coronavirus RaTG13³. Conceptually, an outbreak caused by an emerging zoonotic bat virus has not only been predicted, but expected^{4–6}. Continued human interference with natural ecosystems has resulted in many outbreaks in the past few decades⁶. Along with well-known bat-borne viruses such as rabies and Ebola virus^{7,8}, there is a range of diverse coronaviruses in bats that have confirmed spillover potential for severe disease outbreaks—including severe acute respiratory syndrome coronavirus (SARS-CoV) (which emerged in 2003) and ongoing outbreaks associated with Middle East respiratory syndrome coronavirus (MERS-CoV) (since 2012). The ability of bats to harbour many viruses—and zoonotic coronaviruses in particular—may result from their ability to efficiently regulate host responses to infection, although species richness may also have a role⁹. Through ecological factors, biological traits or their underlying unique immune systems, bats can prevent excessive immune pathology in response to most viral pathogens. Examining these processes will unlock key lessons for human health, from understanding ageing to combating cancer and infectious diseases.

Basic biology of bats

Across mammalian orders, Chiroptera (bats) is a species-rich taxon that stands out as it is uniquely capable of powered flight; bats represent 1,423 of the more than 6,400 known species of mammal^{10,11} (Table 1). This diversity is matched by their wide geographical distribution, which spares only the polar regions, extreme desert climates and a few oceanic islands¹². Bats are keystone species upon which other fauna and flora are highly dependent for fertilization, pollination, seed dispersal and control of insect populations^{13,14}. Bats roost in foliage, rock crevices and caves, and hollowed trees, as well as human-made structures such as barns, houses and bridges¹⁵. Different species may be homo- or heterothermic, using hibernation or shorter, daily episodic torpor to conserve energy¹⁶. Bats are prone to low fecundity and use reproductive strategies such as the storage of sperm or prolonged pregnancies, with either seasonal or aseasonal reproductive cycles¹⁵. Furthermore, they consume a wide range of diets—including nectar, fruit, pollen, insects, fish and blood (as in the common vampire bat (*Desmodus rotundus*)). Ever intriguing to humankind, bats possess the sensing powers of echolocation and magnetoreception (the ability to differentiate polar south from north), both of which are used primarily by microbats^{17–19}. Differences in ecology, biology and physiology are important factors that must be considered in species-specific responses within bats and in the conduction of experimental studies.

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Table 1 | Natural history and physiological traits of bats

Bat traits		
Natural history	Evolutionary age	64 million years ¹⁴⁹
	Number of species	1,422 ¹¹
	Geographical distribution	Every continent except the polar regions and several oceanic islands ¹²
	Roosting habitats	Foliage, hollowed trees, rock crevices, caves and human structures ¹⁵
	Ecological roles	Pollination, seed dispersal and insect control ¹⁵
	Largest known colony size	20 million bats (Mexican free-tailed bat (<i>Tadarida brasiliensis</i>), Bracken Cave (Texas)) ¹⁵⁰
	Diet	Fruit, nectar, pollen, insects, rodents, amphibians, fish and blood ¹³
	Reproductive patterns	Bimodal, seasonal or aseasonal breeding ¹⁵¹
	Thermoregulation	Homeothermy, heterothermy, torpor and hibernation ^{16,152}
	Mode of orientation to space	Visual, echolocation and magnetoreception ^{17–19}
	Lifespan record	≥41 years (a Brandt's bat (<i>Myotis brandtii</i>), from Siberia) ²⁹
	Body size (wingspan)	29 mm to 1.7 m ¹⁵³
	Weight range	2 g to 1.6 kg ¹⁵³
	Hibernating body temperature	≤5.8 °C ¹⁵⁴
	Hibernating heart rate	10–16 beats per minute ^{16,155}
Flight and migration	Migratory distances	Up to 2,000 km ¹⁵⁶
	In-flight body temperature	≥41 °C ¹⁵⁷
	In-flight heart rate	≤1,066 beats per minute ²⁴
	Energetic demands	Up to 1,200 calories per hour ²²
Physiological adaptations	Comparative metabolic rates	2.5–3× higher than similar-sized exercising mammals ²¹
	In-flight increase in metabolic rate	Up to 34× basal metabolic rate ²¹
	Oxidative phosphorylation	Positive selection in 23.08% mitochondrial, 4.90% nuclear-encoded OXPHOS genes ^{83,111}

Despite the advantages and efficiency of aerial transport, flight is a metabolically costly mode of locomotion²⁰: the metabolic rates of bats in flight can reach up to 2.5–3× those of similar-sized exercising terrestrial mammals²¹. This enormous energy demand results in the depletion of up to 50% of their stored energy in a day—nectarivorous bats catabolize their high-energy diet of simple sugars as rapidly as 8 min after consumption, and flying bats consume about 1,200 calories of energy per hour^{22–24}. Bats possess several metabolic adaptations and optimized airflow patterns to circumvent high-energy expenditures that could otherwise lead to starvation and death²⁵. A key adaptation is the marked alteration of heart rate, which increases by 4–5× during flight to a maximum of 1,066 beats per minute²⁴. To compensate for high levels of cardiac stress, cyclic bradycardia is induced for 5–7 min several times per hour during rest, which may conserve up to 10% of available energy. Despite their high metabolic rates and small statures, bats live substantially longer than non-flying mammals of similar body mass^{26,27}. When adjusted for body size, only 19 species of mammals are longer-lived than humans: 18 of these species are bats (the other is the naked mole-rat)²⁸. On average, the maximum recorded lifespan of bats is 3.5× that of a non-flying placental mammal of a similar size²⁹. As a mammalian model of antiageing, bats may offer vital clues in human attempts to delay mortality and enhance longevity.

Status of bats as a unique viral reservoir

Bats have been associated with infectious diseases for centuries. Their role in the transmission of rabies virus led Metchnikov to investigate fruit bat macrophages and their immune responses in 1909³⁰. More recently, several new or re-emerging viral outbreaks associated with spillover from bat reservoirs have been documented, and a number of reports have highlighted the risk of future spillover events into human populations. Enveloped, positive-sense single-stranded RNA coronaviruses are widespread in animals (54% of those known are associated with bats), and cause mild-to-severe respiratory or enteric disease in

humans³¹. The association between coronaviruses and bats began to be recognized with the discovery of SARS-related coronaviruses in bats^{32–35}. Since then, bats have been identified as the richest source of genetically diverse coronaviruses³⁶, including the MERS-CoV-like viruses³⁷ and a range of bat coronaviruses^{38–40}. Several genome sequences of bat coronaviruses have recently been reported that show a high genetic similarity to SARS-CoV-2^{3,41}. The increasing number of spillover events of bat viruses—and of coronaviruses in particular—is believed to stem from the disruption of the natural ecosystems that host bats through climate change, increased urbanization pressure from humans, wildlife trade and animal markets^{34,42,43} (Fig. 1). Some large global initiatives have been funded to examine the risk factors for potential spillover events, but the funding of this area of research has been reduced in recent years^{44,45}. Although an event such as COVID-19 has increasingly been anticipated, few scientists would have expected the magnitude and speed of spread of this current pandemic.

It should also be emphasized that bat-borne viruses cause devastating outbreaks not only in humans, but also in animals such as pigs and horses^{46–49}. During a large-scale outbreak (as with the current COVID-19 pandemic), there is a risk of spillback or 'reverse' zoonotic (anthropozoonotic) transmission from human to animals, as has been demonstrated by COVID-19 outbreaks in minks on two farms in the Netherlands, followed by animal-to-human transmission of the SARS-CoV-2 virus⁵⁰. Anthropozoonotic infections of SARS-CoV-2 have also been observed from pet owners to domestic cats and dogs^{51,52}, and to tigers and lions housed in zoos⁵³. There is a predicted risk of the spread of SARS-CoV-2 to other free-ranging mammalian wildlife, including the great apes⁵⁴ and bats in different geographical locations⁵⁵, and this perceived threat has affected the wildlife tourism industry in many countries. Although intermediate hosts such as civets and pangolins have been implicated in SARS-CoV and SARS-CoV-2 outbreaks (respectively), these animals exhibited pulmonary oedema and inflammation in response to infection with SARS-CoV-2-related coronaviruses^{56–58}, which suggests that they are not true reservoirs for these coronaviruses. By contrast, bats

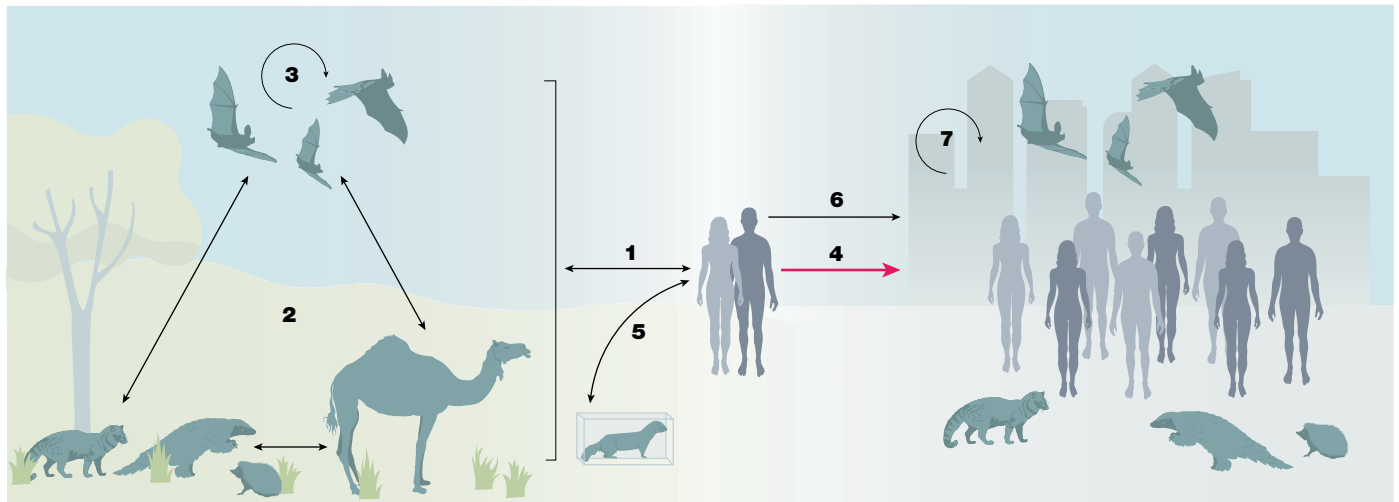


Fig. 1 | The potential zoonotic transmission cycle for coronaviruses.

Coronaviruses may transmit naturally (black arrows) among humans, bats and other wildlife (such as racoon dogs, hedgehogs, pangolins, palm civets, camels (as is known for MERS-CoV) and mink)¹⁵⁸. Human interventions may amplify the spread (red arrow). Transmission cycles may be amplified in urban areas that are normally at a minimal risk of exposure, increasing transmission to humans and accelerating an outbreak scenario. (1) Natural zoonotic infection cycles from domestic animals or wildlife (including bats) to humans and vice versa; human populations at risk include bat guano farmers, or individuals living and working in areas that overlap with bat habitats. (2) Natural enzootic cycle

between different species of wildlife (including bats), and domestic animals and wildlife. (3) Amplification and spread between overlapping bat populations—as, for example, seen among species in the Rhinolophidae and Hipposideridae for SARS-related coronaviruses¹⁵⁹. (4) Amplified zoonotic infections and spread to urban areas via human interventions, including wildlife trade and increased urbanization. (5) Anthrozoönotic infections from humans back to domestic animals or wildlife (for example, as in mink farming⁵⁰). (6) Human migration patterns facilitate spread to urban areas (for example, during holiday seasons¹⁶⁰). (7) Amplified viral spread among humans or animals and humans in dense urban settings.

lack clinical signs of disease when infected with the majority of viruses, although there are some rare exceptions. High-titre infection with Tacaribe virus⁵⁹ or infection with species-divergent strains of lyssavirus⁶⁰ can cause severe symptoms and death. The filovirus Lloviu virus is associated with the death of bats in Spain⁶¹ and the fungal white-nose syndrome kills bats by affecting energy needs as bats awake from hibernation or torpor⁶².

The unique status of bats as a viral reservoir is further confirmed by the fact that bats host more zoonotic pathogens than any other known mammalian species^{63–65}. Previous reviews have discussed the biological traits of these flying mammals and how these traits may empower bats to act as exceptional reservoirs^{4,6,66–68}. Some putative explanations for reservoir potential propose that immune variation during hibernation⁶⁹ or the higher temperatures that bats experience during flight (in the ‘fever’ hypothesis⁷⁰) decrease viral loads and therefore maintain their status as a viral reservoir. However, studies on bat cells grown at high temperatures do not show a decrease in viral titres compared to cells grown at 37 °C⁷¹. In addition, these hypotheses have lost traction recently as more studies indicate a tolerance of virus infection rather than an active reduction of viral load. Recent work on bat metabolism, mitochondrial dynamics, innate and adaptive immunity and links between metabolic and immune systems have provided insights into the potential dynamic responses in bats. What makes bats special might not be their antiviral ability, but rather their antidisease features^{72–74}. Here we hypothesize that the unique balance between host defence and immune tolerance in bats may be responsible for the special relationship between bats and viruses (particularly coronaviruses).

A balanced host defence–tolerance system

Homeostasis is the ultimate state of health for any living system, from cells to human bodies, and obtaining homeostasis requires the constant adjustment of biochemical and physiological pathways. For example, the maintenance of a constant blood pressure results from fine

adjustments to and balancing of many coordinated functions that include hormonal, neuromuscular and cardiovascular systems. This is also true of an effective host defence system. Although an appropriate level of defence is required to combat pathogens and diseases, excessive or dysregulated responses lead to cellular damage and tissue pathology. Many emerging bat-borne viruses—including SARS-CoV and Ebola virus—are highly pathogenic in humans, which correlates with an aberrant innate immune activation with prolonged and/or stronger immune responses^{75–78}. By contrast, infected bats show no or minimal signs of disease even when high viral titres are detected in tissues or sera, which suggests that they are tolerant of viral diseases^{79–82}. Recent studies have provided insights into the mechanisms used by bats to fine-tune a balance between protective versus pathological responses, which may contribute to their extraordinarily long lifespans and low incidence of cancer (Fig. 2).

Enhanced host defence responses

The unique status of bats as a viral reservoir has triggered increasing interest and efforts to characterize the immune system of bats. Earlier efforts focused on genomic^{73,83} and transcriptomic analysis^{84–86}, and particularly on interferon and antiviral activities^{87–90}. Humans express minimal baseline levels of type I interferons (IFNs), and they are highly inducible upon stimulation⁹¹. By comparison, the black flying fox (*Pteropus alecto*) constitutively expresses some baseline IFN α , and many species of bats express several IFN-stimulated genes before stimulation^{84,89,92,93}. This may be regulated by IFN regulatory factors (IRFs), as differential expression patterns of IRF7⁹⁴ and enhanced IRF3-mediated antiviral responses⁹⁵ are observed in bats. The restricted induction of type I IFNs would minimize production of inflammatory cytokines⁹³. The kinetics of the IFN response in bats also differs from those of other mammals, with a faster decline phase for some bat interferon-stimulated genes⁸⁸. In addition, several antiviral genes—such as *RNASEL*^{88,90}—are IFN-induced in bats but not in other mammals^{84,93} or have undergone selection pressure to potentially alter function, such as those encoding Mx proteins⁹⁶ and *APOBEC3*⁹⁷. Antiviral immune activation in bats has



Fig. 2 | The unique balance between host defence and immune tolerance in bats. Bats show an excellent balance between enhanced host defence responses and immune tolerance through several mechanisms. Examples of enhanced host defences include constitutive expression of IFNs and interferon-stimulated genes (ISGs), increased expression of heat-shock proteins (HSPs), a higher base level expression of the efflux pump ABCB1 and enhanced autophagy. On the other hand, dampened STING and suppressed inflammasome pathways—such as dampened NLRP3, loss of PYHIN and downstream IL-1 β —contribute to immune tolerance in bats.

also previously been reviewed^{98,99}. Just as IFN signalling varies across mammals¹⁰⁰, there is likewise variation in the IFN response across bat species. For instance, *P. alecto* shows a contraction of an IFN locus⁸⁹, whereas the Egyptian fruit bat (*Rousettus aegyptiacus*) exhibits no constitutive IFN but has one markedly expanded IFN locus—especially for IFN ω ⁷³. Several species suggest a restricted induction profile of IFN α and IFN β compared to human or mouse^{84,92,93}. Dysregulation of the IFN response has previously been implicated in autoimmune diseases¹⁰¹ and the pathogenesis of several bat-borne viruses, including Ebola virus⁷⁶, SARS-CoV^{75–77} and SARS-CoV-2^{102,103}. Together, these bat-specific changes in baseline expression, kinetics, induction or functions of antiviral genes in IFN signalling could help bats to efficiently control the numerous viruses that they host.

In addition to the innate immune responses, recent studies have shed light on other mechanisms of bat host defence. Enhanced autophagy has a key role in the increased clearance of lyssavirus from bat cells¹⁰⁴, and is known to regulate immunity and mediate pathogen clearance¹⁰⁵. Bats express very high levels of heat-shock proteins, which confers upon bat cells the ability to survive at high temperature and high oxidative stress *in vitro*. Heat-shock proteins contribute to the rapid acceleration of viral evolution by chaperoning viral proteins and tolerating some viral mutations¹⁰⁶. They also act as a viral receptor¹⁰⁷, regulate inflammation¹⁰⁸, block apoptosis¹⁰⁹ and affect ageing¹¹⁰.

Common to all bats yet examined, mitochondrial and nuclear oxidative phosphorylation genes show evidence of specific adaptive evolutionary changes that support the large metabolic demands associated with flight^{99,111}. Bats also have a concentration of positively selected genes in the DNA-damage checkpoint pathways that are important for cell death, cancer and ageing, in addition to the innate immune pathways⁸³. A recent study has demonstrated that efficient drug efflux through the ABCB1 transporter in bats blocked DNA damage induced by the chemotherapeutic drugs doxorubicin and etoposide, conferring resistance to genotoxic compounds, regulating cellular homeostasis and possibly lowering the incidence of cancer¹¹². Bats have a reduced production of reactive oxygen species compared to similar-sized non-flying mammals, but retain intact activity of the important antioxidant superoxide dismutase^{113,114}. These findings suggest either a more effective scavenging of reactive oxygen species or a lower production of reactive oxygen species by bat mitochondria: a recent study has confirmed decreased generation of reactive oxygen species in bats, without the age-dependent decline of antireactive oxygen species defence seen in mice¹¹⁵.

Mechanisms of immune tolerance

Both naturally infected and experimentally infected bats indicate tolerance of viral infection, even during a transient phase of high viral titres^{79–82}. For instance, the infection of bats with high doses of Ebola virus⁷⁹ and MERS-CoV⁸¹ caused minimal or no clinical disease, although

titres can reach as high as 10^7 fluorescent focus-forming units per millilitre of sera for Ebola virus and 10^7 median tissue-culture infectious dose (50% reduction) equivalents per gram of lung tissues for MERS-CoV. This supports an immunological tolerance to RNA viruses in bats, particularly during the acute response. These observations have triggered increasing efforts to study how bats limit excessive or aberrant innate immune responses. From the initial characterization of two divergent bat genomes⁸³ and through more recent genome additions^{73,116,117}, a consistent trend for the evolution of immune-related genes—including those encoding the pattern recognition receptors—has been revealed. Pattern recognition receptors sense endogenous molecules from damaged cells and structurally conserved microbial structures, known as damage and pathogen-associated molecular patterns, respectively¹¹⁸. The recognition of viral invasion by these pattern recognition receptors and their downstream signalling are key first-line defences¹¹⁹. The first mechanistic study of immune tolerance in bats showed that the STING-dependent type I IFN response was dampened in several bat species, and that this results from a point mutation of a highly conserved residue of STING⁸⁷. STING is an important pattern recognition receptor that mediates cytosolic-DNA-induced signalling and has a key role in infection, inflammation and cancer¹²⁰. This mutation might be driven evolutionarily to tolerate the overactivation of STING by host DNA damage that is induced by flight. However, the effect of dampened STING on responses to infection with bat-borne RNA viruses—which might activate STING by inducing host DNA damage¹²¹—is yet to be understood.

A more recent study has revealed a key mechanism by which bats naturally dampen host inflammation in response to ‘sterile’ danger signals and infections with three types of RNA virus (including MERS-CoV)⁷². NLR-family pyrin domain containing 3 (NLRP3), a key inflammasome sensor that recognizes various cellular stresses and pathogen invasions, is dampened at both the transcription and protein level in bats. Importantly, reduced NLRP3-mediated inflammatory responses to RNA viruses have no, or minimal, effect on viral loads. This supports an enhanced innate immune tolerance in bats, which is consistent with their unique status as an asymptomatic viral reservoir. As NLRP3 is increasingly recognized as sensing a broad range of emerging viruses¹²² (including MERS-CoV⁷² and SARS-CoV^{123,124}), this mechanism may have a wide application in the great variety of bat-borne viruses (including SARS-CoV-2)^{125,126}. In addition to NLRP3, an earlier study reported the unique loss of the entire PYHIN gene family at the genomic level in bats¹²⁷. The members of the PYHIN gene family (also known as AIM2-like receptors) including *AIM2* and *IFI16* are recognized as the only inflammasome sensors for intracellular DNA, of both self and microbial origins¹²⁸. Both NLRP3 and AIM2 converge on their downstream effector caspase-1, which is responsible for cleavage of the inflammatory cytokines IL-1 β and IL-18, and simultaneously unleashes inflammatory cell death (pyroptosis) through GSDMD^{129,130}. Recent data reveal additional mechanisms of dampening at the level of downstream caspase-1 and IL-1 β ¹³¹, demonstrating a unique targeting of the inflammasome pathway for inhibition in bats. The high metabolic demands of flight could—in theory—lead to the release of metabolic by-products, including reactive oxygen species, ATP, damaged DNA and other danger signals that are known to trigger inflammasome activation. Therefore, adaptations to flight could have driven the different mechanisms of dampening in bats, which in turn limits excessive virus-induced or age-related inflammation: this could subsequently contribute to the tolerance of viral infection and increased lifespan of bats.

Other studies have provided more insight into the immune tolerance of bats, although these lack functional validation or examination across several bat species. Treatment with polyinosinic:polycytidylic acid—a double-stranded RNA ligand—in cells of the big brown bat (*Eptesicus fuscus*) did not elicit a robust *TNF* induction, owing to a c-Rel motif in the promoter region¹³². However, this might be a species-specific and/or ligand-specific observation, as this motif is not detected in the *TNF*

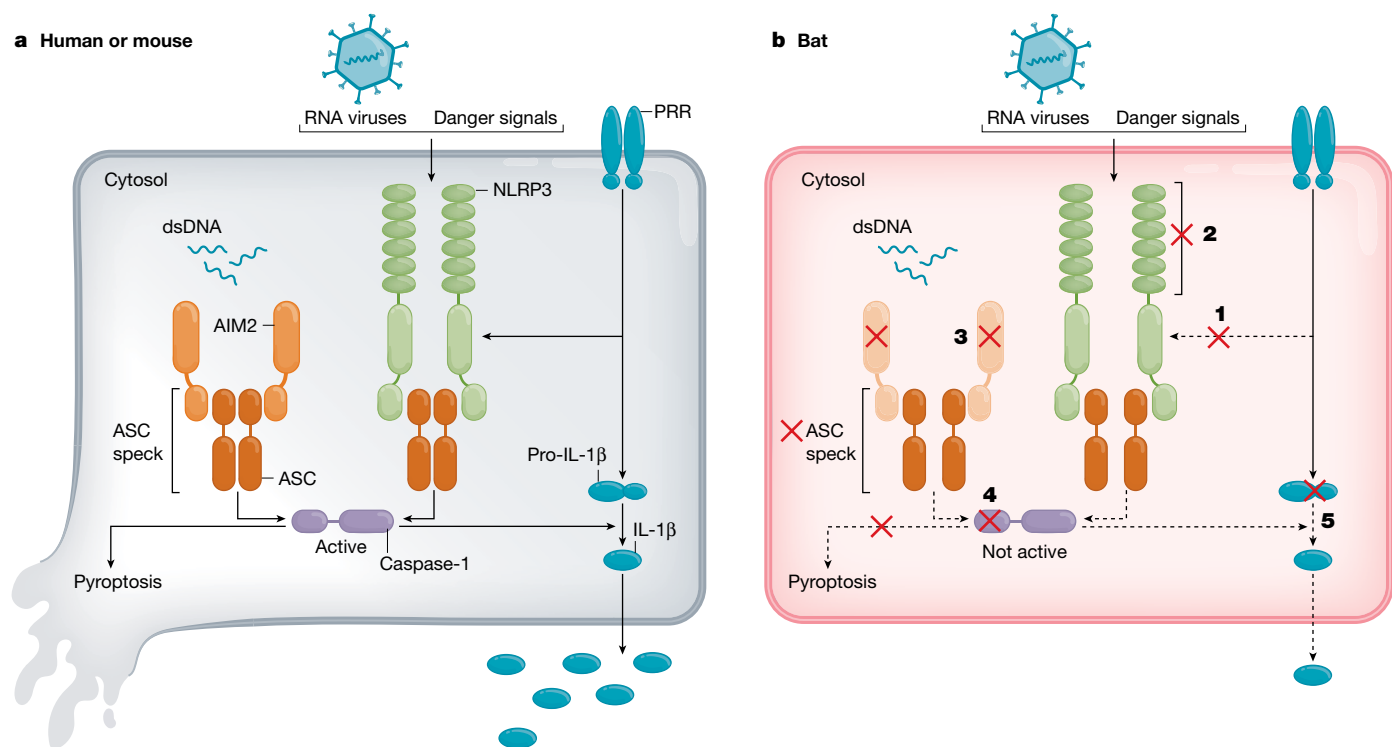


Fig. 3 | Schematic of the multilevel mechanisms of dampened inflammasome activation in bats. a, In human or mouse, pattern recognition receptor (PRR) priming and subsequent activation by RNA viruses, danger signals or intracellular double-stranded DNA activate the NLRP3 or AIM2 inflammasome with intact ASC speck formation, pyroptosis and IL-1 β

secretion. **b**, By contrast, bats have dampened transcriptional priming (1) and reduced protein function (2) for NLRP3, loss of PYHIN including AIM2 (3), and reduced caspase-1 activity (4) and/or IL-1 β cleavage (5), which leads to an overall reduction in inflammation.

promoter region of *P. alecto* and TNF production was observed with other ligands⁷². An inhibitory immune state of natural killer cells has been inferred from genome analysis of natural killer cell receptors, providing support for enhanced immune tolerance⁷³. In a bat–mouse chimaera model, an immunodeficient mouse reconstituted with a bat immune system appeared to be less prone to graft-versus-host disease than were other chimeric mouse systems reconstituted with immune cells from human and other mammalian animal donors¹³³. Although the detailed immune-tolerance mechanism(s) is yet to be elucidated, the observation is consistent with other discoveries relating to bats having a defence–tolerance system that is more balanced than is typical among mammals.

In summary, the overall enhanced host-defence responses—coupled with immune tolerance or dampening—seem to provide a tight balance in how bats respond to stresses, which is elegantly demonstrated in their responses to viral infections. In addition, evolutionary studies have revealed several genes or pathways that are under strong positive selection in bats, which require further functional investigation. These include the nucleic-acid-sensing Toll-like receptors (another group of pattern recognition receptors), which might reflect altered sensing of pathogens¹³⁴. There is evidence for adaptive evolution in bat cGAS–STING and OAS–RNase L pathways, which potentially alter the ability of bats to activate IFN in response to cellular nucleic acids^{87,135}. *Pteropus alecto* MHC-I molecules exhibit a unique isoform with a three-amino-acid insertion within their peptide-binding groove that leads to distinct peptide binding motifs with a preference for proline at the P Ω site¹³⁶. This unique peptide-binding preference is not responsible for the ability of *P. alecto* MHC-I to accommodate N-terminally extended peptides of up to 15-mers¹³⁷. Other bat species show a similar three- or five-amino-acid insertion, a feature that is not shared by most other

mammals and that may confer advantageous T cell immunity^{136,138,139}. Although the genomic characterization and evolutionary studies of bat MHC-II genes have previously been described, further laboratory investigation is required to evaluate any functional differences from those of other mammals^{140,141}.

Learning from bats

Research in bats and viruses of the past few decades has strengthened the notion that bats are indeed ‘special’ as reservoir hosts for emerging viruses. The next important question revolves around discerning what makes bats special. The unique balance of enhanced host-defence responses and immune tolerance through several mechanisms might be the key to this question. Deeper understanding will provide insights and strategies not only to aid in the prediction, prevention or control of zoonotic virus spillover from bats to humans, but also to potentially combat ageing and cancer in humans. Furthermore, the effect of altered bat immunity on viral evolution may cause enhanced virulence after spillover into hosts with divergent immune systems¹⁴². One of the key findings that has previously been highlighted is the dampened activation of the inflammasome complex in bats. Previous studies have demonstrated altered inflammasome activation in bats, including the loss of the PYHIN gene family¹²⁷, dampened NLRP3⁷² and reduced function of caspase-1 and/or IL-1 β ¹³¹ (Fig. 3). Importantly, the breadth of inflammasome-driven diseases in humans is notable, and often involves excessive activation of this pathway. These diseases include—but are not limited to—autoimmune and autoinflammatory diseases, infectious diseases and several age-related diseases (such as metabolic diseases and neurodegenerative diseases)¹⁴³. Mechanistic studies of immune tolerance may reveal key regulatory factors for the development of targets

and strategies to limit harmful inflammatory responses in humans. A genome-wide comparison of immune-related genes reveals that the phylogenetic relationship between bats and humans is closer than that between humans and rodents¹⁴⁴. This greater similarity consolidates bats as potentially representing powerful model species for the study of viral diseases, ageing and cancer, promoting the translation of findings in bats into clinically relevant treatments.

One of the major challenges for studying bat biology and immunology is that—as they are not yet model species—there are limited tools and reagents for bats. Recent efforts to characterize the bat immune system have led to developments of more bat-specific research tools, including antibodies for immune-cell markers^{144,145} and protocols for the differentiation of primary immune cells¹⁴⁶. In addition, newly developed *in vivo* animal models include a bat–mouse chimaera model¹³³ and transgenic or knock-in mouse models that contain a bat gene. Several research groups now also have captive bat colonies. These are invaluable in investigating the mechanisms of host defence or tolerance and facilitating the translation of lessons from bats. With the establishment of further reagents and tools for bats, we are confident that a deeper understanding of what makes bats special will provide insights and strategies to combat infection, ageing and other inflammatory diseases in humans.

Conclusions

A few decades ago, no one would have predicted that bat research would gain the momentum it has now. In addition to flight, various biological traits make bats unique among mammals. Endeavours such as those of the BatIK consortium¹⁴⁷, and technologies such as single-cell RNA sequencing, will allow unbiased and deeper characterization of bats, bat immune-cell populations and their specific functions and pathways. The host defence–immune tolerance balance of bats confers exceptional health. The identification of the key regulators and machinery that are involved in maintaining this homeostatic balance would provide valuable lessons for controlling and combating viruses, cancer, ageing and numerous inflammatory diseases in humans. Viruses do not recognize borders—and neither do bats. An increased awareness of bat research in alignment with translational outcomes for humans and international solidarity in laboratory and field-based research efforts is needed. By understanding the source of emerging viruses and harnessing knowledge from nature, we can develop approaches to improving the global One Health status¹⁴⁸.

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