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Revising the paradigm: Are bats really pathogen reservoirs or do they possess an efficient immune system?

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

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bats represent **1,423** of the more than **6,400** known species of **mammal**[1]
can be found **everywhere on earth except the poles**

Despite the advantages and efficiency of aerial transport, **flight is a metabolically costly** mode of locomotion[20]: the metabolic rates of bats in flight can reach up to 2.5–3× those of similar-sized exercising terrestrial mammals[21].

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 minute**

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)

Are bats viral reservoir animals?

A reservoir animal is defined as an epidemiologically **connected population** in which the **pathogen** can be **permanently maintained** and from which **infection is transmitted** to the target population (Haydon et al., 2002).

More **than 4,100 bat-associated viruses from 23 viral families were detected in ~200 bat species** (Chen et al., 2014). Of these viruses, more than 100 were identified as important for "emerging and re-emerging human infections" (Calisher et al., 2006; Wong et al., 2007). As we will show later in discussion, however, in a substantial proportion of these cases there is no sufficient evidence to consider bats the reservoir species of these viruses.

Our findings suggest that **in many cases the confidence regarding the bats' role as reservoir animals is not sufficiently supported.** Although we **do not claim that bats are never the origin of human pathogens, we suggest that their role has been consistently exaggerated** and often without the necessary scientific basis.

meta-analysis of the literature and examined the finding for over 100 viruses for which bats have been considered potential reservoirs
significant proportion of the cases (48%) this claim has
been based on the seroprevalence of antibodies or PCR tests, and not on actual virus isolation

Table 1. A literature analysis of 101 viruses for which bats were claimed to be reservoir hosts

No	Virus	Family, genus	Serology	PCR	Isolation	Interesting statements from the original paper	Ref
1	Kolente virus	Alpharhabdovirinae, Ledantevirus	no	no	yes		(Ghedin et al., 2013)
2	Tacaribe viru	Arenaviridae, Bunyavirales	yes	no	yes	It has not been found to infect humans	(Price, 1978b; Downs et al., 1963)
3	Nepuyo virus	Bunyaviridae, Bunyavirus	no	no	no	Most closely related to Nepuyo virus	(Calisher et al., 1971)
4	Guama virus	Bunyaviridae, Bunyavirus	no	no	no		(Epstein and Newman, 2011)
5	Catu virus	Bunyaviridae, Bunyavirus	no	no	no		(Pierlé et al., 2015)

Moreover, many of the reported isolations are unconvincing:
(1) Several viruses were only isolated from a single individual bat (Charlier et al., 2002);
(2) In some cases **isolation was performed from a homogenate** of internal tissues from which transmission is unlikely (e.g., the liver and spleen) and **not from oral swabs or saliva glands, urine, feces, or even blood or sera.** (Mortlock et al., 2015; Hayman, 2016);
(3) **Several of the local viruses were also isolated from other animals in the region, including non-bat-specific ectoparasites**
(4) Some isolations were taken from sick or dead individuals which would probably not have transmitted the disease—sick bats have been shown to remain in the roost and refrain from social interactions

To date, the **evidence regarding the isolation of actual harmful pathogen viruses** in bats is limited, with **only a few well-known cases**, including the **Marburg virus** that was isolated from Rousettus aegyptiacus fruit bats in Uganda (Towner et al., 2009), and **Hendra virus** (HeV) that was isolated from Australian fruit bats.

Moreover, as pointed out by (Scott, 2001)
virus **isolation alone is not sufficient for considering an animal a reservoir, as evidence of transmission is also required.** The mere detection of a virus in bats does not imply that spillover will occur, and many additional biological, ecological, and anthropogenic conditions must be in place for such an event to occur (Markotter et al., 2020). Some human pathogenic viruses are also known to infect and affect bats, including most lyssavirus species (Banyard et al., 2011), Tacaribe arenavirus (Cogswell-Hawkinson et al., 2012), and the Zwiesel bat banyangvirus (Kohl et al., 2020), among others that are known to harm bats.

According to (Olival et al., 2017) not **only bats but also primates and rodents have a higher proportion of observed zoonotic viruses compared to other groups of mammals**. Species in other orders (e.g. Cingulata, Pilosa, Didelphimorphia, Eulipotyphla) also share a majority of their observed viruses with humans, but the data is limited in these less diverse and poorly studied orders.

Unraveling the unique bat immune system

Bats have demonstrated a highly diverse antibody repertoire,
exceeding that of most species and on a par only with humans and mice,

Several of the early publications already provided initial evidence of one of the main characteristics of the bat immune system—a delayed immune response, on which wewill elaborate later in discussion. McMurray and Thomas (McMurray and Thomas, 1979) and Paul (Paul and Chakravarty, 1986) found that T-cell proliferation as part of the immune response peaked at 120 h post-infection in comparison to 48 h in mice. Moreover, Chakraborty (Chakraborty, 1983) **found that cell-mediated immunity in bats is slower than in other mammals**. Prolonging the immune response was later found to be a beneficial antiviral strategy in bats (Hayman, 2019).

The strenuous and prolonged physiological efforts exerted during flight impose oxidative stress, resulting in severe DNA damage and the release of self-DNA fragments into the cytoplasm (Barzilai et al., 2002), somewhat similar to the DNA damage caused by a viral infection. Consequently, evolving an **efficient DNA repair mechanism aimed at dealing with flight-induced cellular damage might have also enabled bats to fight off viral infections. Zhang et al. further hypothesized that these mechanisms may also be involved in the unique longevity of bats.**

Interestingly, **one of the most important viral defense lines, namely the interferon (IFN) system, has been shown to vary greatly among bat species** (Clayton and Munir, 2020).

Interferons (IFNs) are secreted cytokines that induce an antiviral response by the host and are primarily responsible for inhibiting viral replication.

New research has revealed **a species-specific gene length size in bats, with much variability in functional responses, including permanent vs. stimulation-dependent secretion of IFNs, with different effects on the immune response:**

1. Type I IFN locus has shortened in Pteropus Alecto (Zhou et al., 2016), but expanded in Pteropus vampyrus and Myotis lucifugus (Pavlovich et al., 2018);
2. Zhou et al., 2016) found a contraction of the type I IFN locus in the Australian black flying fox (P. alecto) and an unusual constitutive expression of IFN-a in these bats. Moreover, IFN type 3 in the same bat was induced in response to a viral infection;
3. Pavlovich et al., 2018) found a type I IFN complex in Rousettus bats, revealing an inhibitory signaling potential with no constitutive expression;
4. Banerjee et al., 2017) showed that while poly I:C treatment (imitating dsRNA stimulus which is usually associated with viral infection) induces the secretion of type I IFNs in both human and Eptesicus fuscus bat cells, the bat cells express much lower levels of these inflammatory mediators; and
5. Sarkis (Sarkis et al., 2018) found the induction of selective IFN stimulated genes in the common vampire bat (Desmodus rotundus). Some of these versatile responses led to the realization that the antiviral state achieved by a variety of IFN phenotypes in bats is lso related to an anti-inflammatory response

Humans express
minimal baseline levels of type I interferons (IFNs), and they are highly inducible upon stimulation[91]**. By comparison, the black flying fox (*Pteropus alecto*) constitutively expresses some baseline IFNα, 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 IRF7[94] and enhanced IRF3-mediated antiviral responses[95] are observed in bats. The restricted induction of type I IFNs would minimize production of inflammatory cytokines[93]

Just as IFN signalling varies across mammals[100]**, there is likewise variation in the IFN response across bat species. For instance, *P. alecto* shows a contraction of an IFN locus**[89]**, whereas the Egyptian fruit bat (*Rousettus aegyptiacus*) exhibits no constitutive IFN but has one markedly expanded IFN locus—especially for IFNω**[73]**.**

Pattern recognition receptors sense endogenous molecules from damaged cells and structurally conserved microbial structures, known as damage and pathogen-associated molecular patterns, respectively[118]. **The recognition of viral invasion by these pattern recognition receptors and their downstream signalling are key first-line defences[119]. 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 STING[87]**. STING is an important pattern recognition receptor that mediates cytosolic-DNA-induced signalling and has a key role in infection, inflammation and cancer[120]. **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 damage[121]—is yet to be understood.

The IFN system has also been shown to vary at the genetic regulation level. Xie and Li (Xie and Yang Li, 2020) demonstrated that a **variety of bat species have a dampened interferon response owing to the replacement of the highly conserved serine residue in STING (stimulator of interferon genes), an essential adaptor protein in multiple DNA sensing pathways.** This means that, in these species, the IFN response has substantially diminished, **resulting in a reduced inflammatory response**. Via the IFN antiviral cascade, the balanced reduction of inflammasome has started to be discovered.

Recent findings suggest that **a novel ‘‘trick’’** of the bat immune system might be that of the reduced **inflammatory response that accompanies the antiviral response of the system**. In recent years, evidence is accumulating that in addition to its antiviral abilities, the bat immune system is characterized by a **general restrained response during inflammatory processes.** One mechanism responsible for reducing the immune response is that of the complete and **unique loss of the PYHIN gene** that was found in P. alecto and M. davidii bats (Ahn et al., 2016). **This family of proteins serves as important immune sensors of intracellular self and foreign DNA and as activators of the inflammasome and/or interferon pathways.** This reduction aids in achieving a milder inflammatory response. Another example of a dampened pathway is related to the important inflammasome sensor NLR family pyrin domain-containing 3(NLRP3), which has been linked to both viral-induced and age-related inflammation. Ahn et al., 2019 found a dampened NLRP3-mediated inflammation in P. alecto, with implications for longevity and unique viral reservoir status. Recently, a diminished inflammatory signaling pathway was found in P. alecto and M. davidii bats (Goh et al., 2020).

As nicely summarized by Schneider et al. (Schneider and Ayres, 2008) there are two ways to survive infection: resistance and\or tolerance. It seems that bats have developed an excellent balance between the two: an enhanced host defense response, and immune tolerance through several different mechanisms (see (Irving et al., 2021) for a detailed review article). **Suppressed inflammasome pathways—as noted above—contribute to immune tolerance in bats and a well-balanced reaction.** In humans, the dysregulation of the immune system seems to be responsible for increasing the severity of illness in the acute phase of viral disease (Hope and Bradley, 2021). Bats, in contrast, contend better with deadly viruses and, despite a longer or slower time of reaction, they eventually overcome these viruses to reach full recovery and elimination of the pathogen. Recent studies have focused on bats' ability to contend with some of the most notorious viruses, including Marburg virus (Guito et al., 2021), COVID-19 (Ruiz-Aravena et al., 2022), and others (Mandl et al., 2018). A restrained immune response has also been shown to be valuable regarding longevity (Kacprzyk et al., 2017; Gorbunova et al., 2020).

When considering the interaction of bats with viruses, the time seems right for a paradigm shift. **Many bats contend with a variety of deadly viruses better than other mammals**. This ability has evolved over nearly 60 million years of adaptation to powered flight. **Bats balance their immune response in such a way that it is slow but highly efficient, making them seropositive and immune to viruses.** Following immunity, their chance of relapse, to the point of becoming contagious, is low. This is evident from the numerous studies cited above, which have not managed to isolate a viable virus from antibody-seropositive bat individuals; and it is also evident from intentional bat infections in which the virus was shown to disappear after up to one month. **In most cases, bats thus carry and spread infectious agents during the limited time frame of their sickness before they overcome it. A spillover of viral pathogens can only occur when bats harbor the identical human pathogenic virus. However, many viruses carried by bats cannot infect humans without first undergoing a natural process of evolution, meaning that bats carry the ancestral viruses and not the human pathogen**