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Review

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

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SUMMARY

While bats are often referred to as reservoirs of viral pathogens, a meta-analysis of the literature reveals many cases in which there is not enough evidence to claim so. In many cases, bats are able to confront viruses, recover, and remain immune by developing a potent titer of antibodies, often without becoming a reservoir. In other cases, bats might have carried an ancestral virus that at some time point might have mutated into a human pathogen. Moreover, bats exhibit a balanced immune response against viruses that have evolved over millions of years. Using genomic tools, it is now possible to obtain a deeper understanding of that unique immune system and its variability across the order Chiroptera. We conclude, that with the exception of a few viruses, bats pose little zoonotic danger to humans and that they operate a highly efficient anti-inflammatory response that we should strive to understand.

INTRODUCTION

Bats (Chiroptera) comprise the only order of mammals with the ability for powered flight, and with nearly 60 million years of physiological adaptions for this ability (Lei and Dong, 2016). With over 1,400 species, bats account for more than 20% of all mammalian species, second only to rodents, and can be found everywhere on earth except the poles (Calisher et al., 2006). Bats play an important role in insect control, reseeding deforested areas, and pollinating a variety of plants (Boyles et al., 2011; Zaho, 2020). Despite these useful roles, bats are mostly perceived as posing a threat to public health, as major transmitters of pathogenic and potentially zoonotic viruses (Dobson, 2005; Leroy et al., 2005; Li et al., 2005; Calisher et al., 2006). COVID-19 is only one recent example of media reports (Zhou et al., 2020) connecting bats to human disease and targeting them as reservoir animals, despite a lack of evidence (Andersen et al., 2020). Although the coronavirus isolated from bats in Wuhan (China) was found to be 96% genetically identical to the beta coronavirus that started the current pandemic, this degree of similarity accounts for a temporal distance of several to many years between the two, when taking the mutation rate of the virus into account (Boni et al., 2020; Ruiz-Aravena et al., 2022). Notably, the receptor-binding domain (RBD) of the bat virus cannot bind to human cells, indicating that it is not the direct source of the pandemic (Andersen et al., 2020; Chan et al., 2020; Ruiz-Aravena et al., 2022). Although there is some evidence that the potential ancestral COVID-19 virus had originated in bats (Shereen et al., 2020), to date, two years after the pandemic first struck, we still do not know the direct source of the human pathogenic COVID-19 variant (Ruiz-Aravena et al., 2022; Frutos et al., 2022). The bats' widespread image as a danger to public health will, however, be difficult to rehabilitate (Zaho, 2020; MacFarlane and Rocha, 2020). In this review, we scrutinized the literature in order to assess the evidence and determine whether bats are or are not reservoir animals for more than a hundred pathogenic viruses, as is often claimed (Calisher et al., 2006; Epstein and Newman, 2011; Hayman, 2016; Wang and Anderson, 2019). 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.

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). A slightly broader interpretation of this term is discussed by Ashford (Ashford, 2003).

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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 also related to an anti-inflammatory response (see more in this recent review (Clayton and Munir, 2020).

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.

A restrained immune response serves better in contending with viruses

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).

Conclusions

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 (Forni et al., 2017; Clayton and Munir, 2020; Latinne et al., 2020). This is also what is known so far for COVID-19 (Poon et al., 2004; Boni et al., 2020; Ruiz-Aravena et al., 2022; Frutos et al., 2022). We should seek to avoid the disruption of their natural habitats that are resulting from rapid urbanization,