


VIEWPOINT

Translation from bats to humans beyond infectious diseases

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Bats are attracting the greatest attention recently as a putative reservoir of SARS-CoV-2 responsible for the COVID-19 pandemic. However, less known to the public, bats also have several unique traits of high value to human health. The lessons we learn from bats can potentially help us fight many human diseases, including infection, aging, and cancer.

The current coronavirus disease 2019 (COVID-19) pandemic has led to more than 170 million cases and 3 million deaths worldwide. It has caused significant morbidity and mortality with enormous economic, societal, and public health impact. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for this unprecedented outbreak, is shown to have an ancestral origin in bats, with 96% identity to a bat CoV (Zhou et al., 2020). Even before COVID-19, bats had already attracted increasing attention from both public and scientific arenas as a special viral reservoir (Olival et al., 2017). In fact, bats are the richest source of CoVs, including SARS-CoV, Middle East respiratory syndrome CoV, and many other bat CoVs (Hu et al., 2021). They also host other high-profile viruses like Hendra virus, Nipah virus, and Ebola virus (Wang et al., 2020). Importantly, many of these emerging viruses are highly pathogenic or lethal in humans and yet cause no or minimal signs of disease in bats, even with a high viral load. Bats also have an exceptionally long lifespan and are likely more resistant to cancers. These biological features with high value to humans have triggered great interest and efforts to study bat biology, especially the bat immune system. Recent progresses started to shed new lights on the underlying mechanisms of disease resistance (Irving et al., 2021). A deeper understanding of what makes bats

special is timely and significant, as these lessons from bats could be translated into new strategies, targets, and ultimately, therapies for many human diseases.

Why bats?

Bats are ecologically, biologically, and geographically diverse and are the second most species-rich mammalian group after rodents, with over 1,400 species. The most remarkable trait among all, distinguishing them from all other mammals, is their ability of powered flight. Flight, as a very efficient type of locomotion, has extremely high energy demand and is more metabolically “costly” than any other mode of locomotion in vertebrates. During flight, metabolic rates can reach >34 times the resting state, with a heart rate of >1,000 beats per minute and a high body temperature >40°C (Thomas and Suthers, 1972). In spite of the highly elevated metabolic rate and heart rates, bats are extremely long-lived relative to their body mass. According to the traditional “rate-of-living” theory, a higher metabolic rate, which is associated with a smaller body mass, correlates with a shorter lifespan. However, bats are clearly “outliers” in the linear relationship between longevity and body mass of mammals (Fig. 1, A and B). Their lifespan is strikingly on average 3–4 times longer and up to 10 times longer than terrestrial mammals of a similar size like mice, with the

oldest bat being more than 41 yr old but weighing only ~7 g (Wilkinson and South, 2002). Most bat species have only one or two reproductive cycles per year and typically produce one pup, bearing more resemblance to humans than mice (Fig. 1 C). Related to an elongated lifespan, anecdotal evidence suggests a lower rate of tumorigenesis than most of other mammals (Wang et al., 2011).

Other than the unique flight ability, the status of a “special” reservoir for emerging zoonotic viruses is perhaps most well-known, due to many high-profile viruses, including the COVID-19 virus. Although it was once under debate over decades, recent studies and analyses have come into a growing consensus that bats are indeed special viral reservoirs (Olival et al., 2017). In addition to the high-impact viruses, bats host a broad diversity of viruses with greater viral richness (that is, the number of unique viral species found in a given host species) and a significantly higher proportion of zoonotic viruses than all other mammalian groups (Fig. 1 D; Olival et al., 2017). Importantly, those viruses that are highly pathogenic to humans or other animals can infect bats and even replicate at a high level in tissues or sera but cause no or minimal signs of diseases (Fig. 1, E and F). These observations support an enhanced tolerance of viral infection or resistance of viral disease, rather than an enhanced antiviral defense in bats. Besides, a few other

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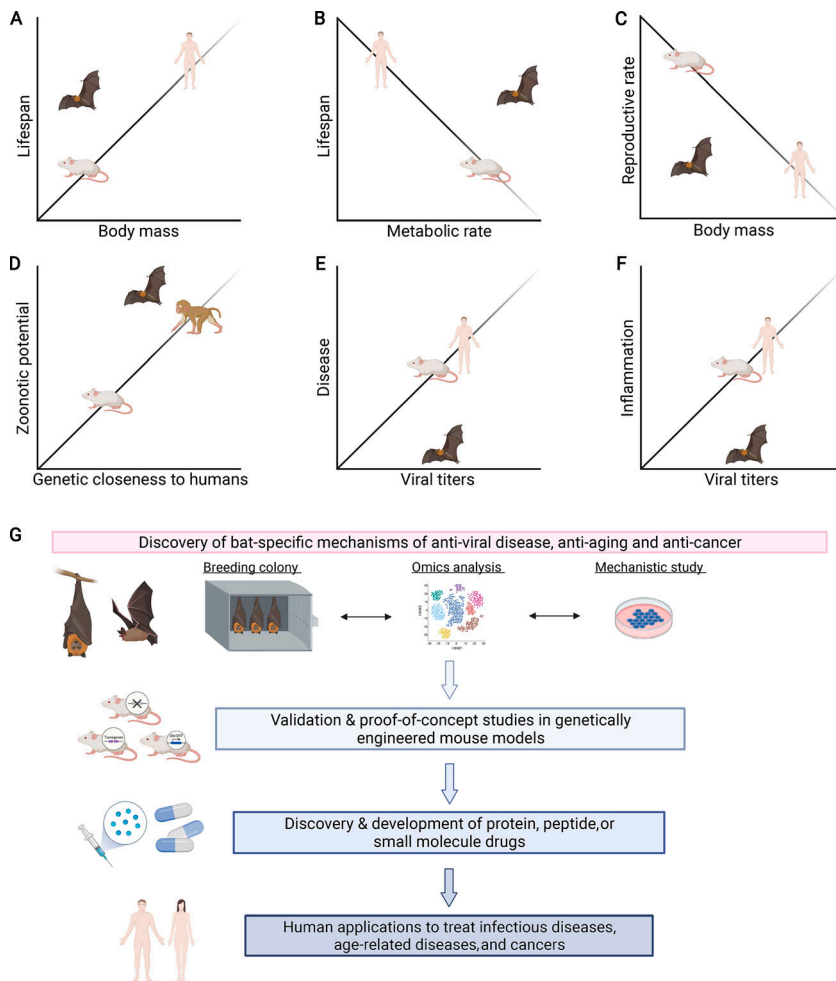


Figure 1. An integrated approach to therapeutic development to fight human diseases based on naturally evolved anti-disease mechanisms in bats. (A–F) Unique phenotypes of bats are shown in the context of a general relationship (diagonal lines) between two of the biological factors among mammals. Humans, primates, and mice are the representative species. (G) A systemic approach to translating discoveries in bats into identifying new strategies or targets and developing new therapeutics to fight a variety of human diseases including infectious diseases, age-related diseases such as metabolic diseases and neurodegenerative diseases, and cancers.

characteristics of bats, including living in large colonies numbering up to 20 million and the ability to travel hundreds of kilometers via flight, might have further made them an exceptional viral reservoir.

What makes bats special?

Although research into the natural mechanisms of disease resistance in bats is still at its infancy, significant breakthroughs have been made in the last decade. Recent studies into bat biology demonstrate a unique balance between enhanced host defense and immune tolerance (Irving et al., 2021). Some examples of enhanced host defense responses include constitutive expression of some IFNs and/or IFN-stimulated genes, higher basal expression of heat-shock proteins (HSPs), an

efficient efflux of genotoxic compounds mediated by the ABCB1 transporter, and age-related increase of autophagy. On the other hand, loss (reduction)-of-function mutation in stimulator of IFN genes (STING) molecule and dampened inflammasome activation are the key examples of immune tolerance in bats. It is noteworthy that pathogenesis of many bat-borne viruses, including Ebola virus, SARS-CoV, and SARS-CoV-2, strongly correlates with an aberrant activation of innate immune response that is excessive and/or prolonged (Mandl et al., 2015). In contrast, bats can effectively control the infection without developing signs of diseases during the acute phase response. This observation led to more in-depth investigation into how bats limit excessive or inappropriate innate

activation, especially host inflammatory responses. Strikingly, recent studies have demonstrated multi-level mechanisms of dampened inflammasome activation in bats, including the genomic loss of PYHIN gene family including AIM2 (Ahn et al., 2016), dampened transcriptional up-regulation and protein function of NLRP3 (Ahn et al., 2019), and reduced activity of caspase-1 and/or cleavage of IL-1 β (Goh et al., 2020). These mechanisms can lead to overall reduction in both virus-induced and age-related inflammation, contributing at least partially to their resistance of viral disease.

Although bats appear to be an excellent model for anti-aging or anticancer research, there have been limited mechanistic studies and few in vivo studies. Recent studies, however, have provided some insights into the potential roles of mitochondrial function, autophagy, telomeres, HSPs, ABCB1 transporter, STING, growth hormone/insulin-like growth factor 1 axis, microRNA, and certain genes in DNA damage checkpoint pathways with altered expression or under strong selection pressure, in cancer resistance and longevity (Foley et al., 2018; Irving et al., 2021; Seluanov et al., 2018). These studies still largely lack functional validation. In addition, there are quite a few important and relevant areas yet to be explored or further studied, such as ROS, immunosenescence, cell cycle or proliferation, and innate lymphoid cells. The high metabolic demand of flight might have triggered significant metabolic stress and release of metabolic byproducts like ROS, ATP, and damaged DNA in ancient bats, leading to immune activation and collateral damage. Therefore, the adaptation to flight could have been the primary driving force for the different molecular mechanisms of unique traits in bats. Such mechanisms can be universal mechanisms shared by all bats or specific strategies harnessed by certain lineage of bats. Some might have pleiotropic effects responsible for more than one phenotype.

How to translate from bats to humans?

The molecular mechanisms of disease resistance in bats are of great value and significance. Although model organisms like rodents and nonhuman primates are well established and commonly used in preclinical studies, they are foremost used to study disease pathogenesis rather than for discovering mechanisms of disease resistance.

As these natural mechanisms have been developed and selected over more than 60 million years, possibly during their adaptation to flight, they are likely very effective and safe. Importantly, in terms of phylogenetic or genetic closeness of whole genomes or immune-related genes, bats actually have a closer relationship with humans than mice do (Fig. 1 D; Gamage et al., 2020). This greater genetic similarity further increases the usefulness and attraction of bat experimental models to translate these mechanisms in bats into clinically relevant treatments in humans.

Several research groups have established captive bat colonies (Fig. 1 G). These include flying foxes, Egyptian fruit bats, cave nectar bats, and Jamaican fruit bats, known to be able to host potentially zoonotic henipaviruses, filoviruses, reoviruses, and arnavirus, respectively. These colonies are invaluable in deriving fresh bat samples and, more importantly, performing in vivo studies. Virus challenge with bat and non-bat viruses will offer greater insights into virological, serological, and immunological aspects of host–pathogen interaction. Non-infectious challenges such as irradiation and tumor xenografts can also be used to study their resistance of cancer. Customized bat diets, matching high-fat or Western-type diets for rodents, can provide opportunity to assess their potential resistance of age-related diseases like prediabetes, obesity, and metabolic syndrome. While longitudinal sampling is helpful for aging studies, an optimal age determination method for long-lived bats would be instrumental in identifying bats of different ages, especially old age, to compare senescence or immunosenescence between bats and humans/mice.

One of the major challenges for bat research has been the lack of bat-specific tools and reagents, especially antibodies for cell markers. To circumvent this obstacle, omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, are being employed to perform high-throughput and in-depth analysis at the molecular level. In particular, single-cell RNA sequencing (scRNA-seq) allows unbiased marker-free decomposition of cells from tissues or peripheral blood to identify

both known and unknown cell types or subtypes and provide direct insight into their functional states. This cellular atlas can guide the development of antibodies against cell-specific markers for downstream functional studies. By analyzing the samples from animal studies, scRNA-seq will reveal in vivo cellular and molecular responses to various stimulation at a high resolution. Subsequent ex vivo or in vitro studies using bat primary or immortalized cells are critical to validate the identified cellular and molecular mechanisms.

These new mechanisms can involve an existing or novel molecule, pathway, or cell subset with loss- or gain-of function or an unknown function. Although genetically engineered bats are unlikely to be realistic in the near future, a few methods such as knockdown of gene expression or depletion of cell subset are potential ways to validate the mechanisms in vivo for bats. However, it is clearly more convenient and efficient to conduct the proof-of-concept studies in mouse by establishing genetically modified mice and examining the disease resistance in relevant disease models (Fig. 1 G). If these animal models show a strong phenotype with an improved disease outcome, pharmacological interventions for preventing or treating infectious diseases, age-related diseases, and cancers can be developed to mimic the natural mechanisms learned from bats. It can be protein- or peptide-based therapeutics derived from a bat protein or a small molecule as a result of target-based or phenotypic drug discovery (Fig. 1 G). For instance, bats have evolved to naturally dampen inflammasome signaling, while targeting inflammasome is recently recognized as new therapeutic avenue for many inflammatory diseases including infectious disease, autoimmune diseases, and many age-related diseases, such as cardiovascular, metabolic, and neurodegenerative diseases. Our group is currently validating some of new mechanisms of inflammasome inhibition, that have naturally evolved in bats, in mouse models and applying these mechanisms in humans through development of protein-based or small molecule drugs.

Studying these non-model organisms can be more challenging and less convenient, but

ultimately is very rewarding. The ongoing efforts and establishments of captive breeding colonies, primary cell or organoid culture, immune cell lines, cell marker antibody, and multi-omics database are critical. With recent technological and scientific advances, it is timely and significant to study more in-depth these exceptionally “healthier” mammals to better understand the underlying mechanisms of their ability to achieve excellent balance in defense versus tolerance. These discoveries could lead to identification of new targets, development of novel strategies, and eventually therapeutics to fight many medically important human diseases from infectious diseases to age-related diseases and cancers.

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