JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 5, 2020

EDITOR'S PAGE

SARS-CoV-2 and Bats

From Flight to Fighting COVID-19

Douglas L. Mann, MD, *Editor-in-Chief, JACC: Basic to Translational Science*

Bats have been getting a lot of bad press lately, following the revelation that the genomic sequence of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) shared 96.2% sequence identity with Bat CoV RaTG13 (1). If one can move beyond the zoonotic public relations nightmare caused by the coronavirus disease-2019 (COVID-19) epidemic, bats present an amazing evolutionary story that may provide insights into the development of new therapeutic approaches for treating COVID-19 patients.

Bats (Chiroptera) represent one of the largest (>1,3000 species) mammalian species, accounting for ~20% of all mammals. What makes bats unique is that that they are the only mammals capable of self-powered flight, which likely explains why bats inhabit every continent except for Antarctica. The earliest known bats likely arose during the Eocene era (49 to 53 million years ago); however, their actual evolutionary history is partially obscured by the paucity of intact fossil records. There have been a number of speculative theories with respect to whether bats evolved the ability to fly first or whether they first developed the ability to listen to the reflected echoes from sounds that they emitted to map out their environment (echolocation). Recent information gleaned from a rare 52-million-year-old bat fossil suggests that flight evolved before echolocation (2). Regardless of which came first, bats have a remarkable capacity for flight, and can achieve speeds of up to 160 km/h (99 miles/h), as well as remain in flight continuously for hours at a time. Germane to this discussion, the evolutionary pressures imposed by flight in bats have selected for a novel suite of antiviral immune responses that control viral propagation, while also limiting self-damaging inflammatory responses. This evolutionary step may have allowed bats to emerge as zoonotic hosts for viruses, including SARS-CoV-1 and -2.

Because bats have high metabolic rates and high body temperatures (often >41°C), they are prone to developing oxidative stress during flight, which can lead to deoxyribonucleic acid (DNA) damage, and initiate brisk inflammatory responses if the damaged DNA leaks into the cytosolic compartment. Selective evolutionary pressures related to flying appear to have positively selected for antioxidant and DNA repair pathways that allow bats to effectively engage tissue repair mechanisms without excessive inflammatory responses. As 1 example, bat cells appear to have a diminished ability to detect endogenous damaged DNA because of mutations in stimulator of interferon genes (STING), which is an endoplasmic reticulum adaptor protein that regulates the expression of type 1 interferon (IFN) host response genes (3). Although this adaptation would not be important in terms of directly preventing pathological immune responses to SARS-CoV-2 (a single-stranded RNA), it is likely important in terms of preventing pathological immune responses to DNA damage after prolonged flight. The STING pathway might also represent a novel therapeutic target in COVID-19 patients, wherein SARS-CoV-2–induced cell death might lead to release of damaged DNA fragments in alveolar cells, resulting in a brisk inflammatory response and collateral tissue damage. Perhaps not surprisingly, biotech companies are targeting small molecule inhibitors of the STING pathway to dampen inflammatory signaling in autoimmune diseases (4). Bats also appear to have developed ways to directly limit viral replication, by enhancing autophagic repair mechanisms (5).

Bats have also developed unique mechanisms that allow them to mount and maintain a strong type I IFN

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.04.012

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 5, 2020
MAY 2020:545–6

response, which is the critical first line of antiviral defense in mammalian cells (3). The initiation of antiviral immune responses begins with the engagement of germ-line encoded pattern recognition receptors that are ubiquitously expressed in mammalian cells. Single-stranded RNA coronaviruses that enter the endosomal compartment of cells initiate antiviral responses by binding to toll-like receptor 7, an endosomal pattern recognition receptor. In the cytoplasmic compartment of the cell, retinoic acid-inducible gene-1 and mitochondrial antiviral signaling proteins are capable of detecting double-strand viral RNA moieties. Following recognition and engagement with viral genomic material, the aforementioned pattern recognition receptors induce the expression of hundreds of type 1 IFN genes that up-regulate cell-intrinsic and -extrinsic antiviral responses. Intriguingly, bats constitutively express IFNα genes in the absence of stimulation by genomic viral RNA or DNA. In other mammalian species, chronic inflammation is associated with a poor prognosis; however, bats have evolved novel mechanisms that limit inflammation-mediated cell damage through up-regulation of inhibitory proteins such as c-Rel, which prevents the activation of nuclear factor-kappa B, a central mediator of cellular inflammatory responses (3). The immune cells of bats have also evolved mechanisms to decrease NLRP3 (nod-like receptor pyrin domain containing 3) inflammasome activation (3). Relevant to this discussion, there are 3 ongoing clinical trials that are evaluating colchicine (which inhibits inflammasome activation) in COVID-19 patients. The largest of these trials is the randomized open-label controlled trial to study the benefit of colchicine in patients with COVID-19 (COL-COVID; NCT04350320). There are also ongoing trials using interleukin-1β antagonists (NCT04330638, NCT04324021), which is 1 of the pro-inflammatory cytokines released secreted by cells following inflammasome activation.

The increasing recognition that bats serve as flying resorts for zoonotic diseases that become lethal when they jump to humans has prompted scientists to embark on a deeper understanding of exactly how bats are able to tolerate viral infections without experiencing disease. While some of the same antiviral strategies that bats employ to modulate viral infections are also being tested in COVID-19 clinical trials (e.g., interferons), we still have a lot to learn with respect to how bats are able to mount brisk antiviral responses without also developing collateral tissue damage secondary to sustained chronic inflammatory signaling. Perhaps one day this type of knowledge might move beyond treating COVID-19 patients and could also be utilized to treat cardiovascular diseases, wherein chronic inflammation results in collateral damage and untoward patient outcomes (e.g., heart failure).

ADDRESS FOR CORRESPONDENCE: Dr. Douglas L. Mann, Editor-in-Chief, *JACC: Basic to Translational Science,* American College of Cardiology, 2400 N. Street Northwest, Washington, DC 20037. E-mail: jaccbts@acc.org.

REFERENCES

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270–3.

2. Simmons NB, Seymour KL, Habersetzer J, Gunnell GF. Primitive Early Eocene bat from Wyoming and the evolution of flight and echolocation. Nature 2008;451: 818–21.

3. Banerjee A, Baker ML, Kulcsar K, Misra V, Plowright R, Mossman K. Novel insights into immune systems of bats. Front Immunol 2020;11:26.

4. McCracken GF, Safi K, Kunz TH, Dechmann DK, Swartz SM, Wikelski M. Airplane tracking documents the fastest flight speeds recorded for bats. R Soc Open Sci 2016;3: 160398.

5. Laing ED, Sterling SL, Weir DL, et al. Enhanced autophagy contributes to reduced viral infection in black flying fox cells. Viruses 2019; 11:1–18.