

Bat and Emerging Infections

Linfa WANG

INFECION 2019, HK 190611



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DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE
(07.2012 -)



CSIRO Australian Animal Health Lab (AAHL)
12. 1990 to 08-2015



Bat facts



- One mammalian species in five (20%) is a bat
- Second to rodents in number of living genera and species
- The only non-terrestrial mammal
- More widely distributed than other mammals, except man
- Variable thermoregulation
- Ecolocation
- Long life span (a 7-gram bat can live up to 41 years!)
- Low rate of tumourigenesis
- Reservoir of a large number of viruses

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25 years of research - 3 questions

- 1) Are bats important viral reservoir?
- 2) Are bats special as viral reservoir?
- 3) What makes bats special?

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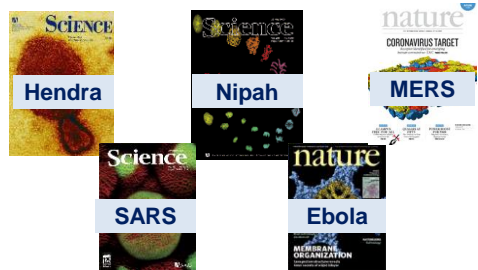
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Hendra virus outbreak in Australia

Time: September 1994
Place: Hendra, Brisbane
Death: 13 horses, 1 human
Infected: 7 horses, 1 human



Bat viruses: They are high impact (factor) pathogens!



BRIEF COMMUNICATION

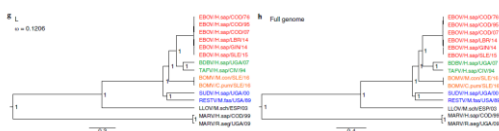
<https://doi.org/10.1038/s41564-018-0227-2>

nature
microbiology

Corrected: Author Correction

The discovery of Bombali virus adds further support for bats as hosts of ebolaviruses

Tracey Goldstein^{1,2,3,4}, Simon J. Anthony^{1,2,3,4,5,6}, Aiah Gbakima³, Brian H. Bird¹, James Bangura¹, Alexandre Tremereau-Bravard¹, Manjunatha N. Belagahanalli¹, Heather L. Wells¹, Jasjeet K. Dhanota¹, Eliza Liang^{2,4}, Michael Grotz², Rohit K. Jangra², Veronica A. DeJesus¹, Goika Lasso², Brett R. Smith¹, Amara Jambal¹, Brima O. Kamara¹, Sorlie Kamara¹, William Bangura¹, Corina Monagle^{1,2}, Sagl Shapira^{1,2}, Christine K. Johnson¹, Karen Saylor^{1,2}, Edward M. Rubin^{1,2}, Kartik Chandran¹, W. Ian Lipkin^{1,2} and Jonna A. K. Mazet¹



LETTERS

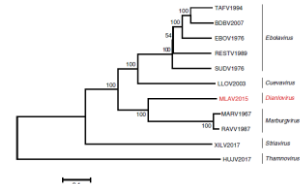
<https://doi.org/10.1038/s41564-018-0228-y>

nature
microbiology

Corrected: Author Correction

Characterization of a filovirus (Mēnglā virus) from Rousettus bats in China

Xing-Lou Yang^{1,2,3}, Chee Wah Tan^{1,3}, Danielle E. Anderson^{1,3}, Ren-Di Jiang^{1,3}, Bei Li¹, Wei Zhang¹, Yan Zhu¹, Xiao Fang Lin¹, Peng Zhou¹, Xiang-Ling Liu¹, Wuxiang Guan¹, Libiao Zhang¹, Shi-Yue Li¹, Yun-Zhi Zhang^{1,3}, Lin-Fa Wang^{1,3} and Zheng-Li Shi^{1,3}



SADS-CoV

LETTER

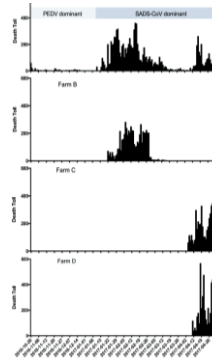


<https://doi.org/10.1038/n41586-018-0010-9>

Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin

Peng Zhou¹, Hang Fan², Tian Lan^{3,4}, Xing-Lou Yang¹, Wei-Feng Shi¹, Wei Zhang¹, Yan Zhu¹, Ya-Wei Zhang⁵, Qing-Mei Xie^{3,4}, Shaohendra Mani⁶, Xiao-Shuang Zheng¹, Bei Li¹, Jin-Man Li¹, Hua Guo¹, Guang-Qian Pei¹, Xiao-Ping An¹, Jun-Wei Chen^{3,4}, Ling Zhou^{3,4}, Kai-Hu Mu^{1,7}, Zuo-Xian Wu^{1,8}, Di Li^{1,9}, Danielle E. Andersen¹, Li-Rao Zhang¹, Shi-Yue Li¹, Zhi-Qiang Mi¹, Tong-Tong He¹, Feng Cong¹, Peng-Ju Guo¹, Ren Huang¹, Yun Luo¹, Xiang-Ling Liu¹, Jing Chen¹, Yong Huang¹, Qiang Sun¹, Xiang-Li-Lan Zhang¹, Yuan-Yuan Wang¹, Shao-Zhen Xing¹, Yan-Shan Chen^{3,4}, Yuan Sun^{3,4}, Juan Li¹, Peter Daszak^{10,11}, Lin-Fa Wang¹⁰, Zheng-Li Shi¹⁰, Yi-Gang Tong^{12,13} & Jing-Xun Ma^{1,4}

Zhou et al., Nature 2018



Are bats special/different?

- Unable/difficult to produce clinical signs in experimental infection of bats with different viruses
- Isolation of viruses from healthy bat primary cells (persistent infection)
- Higher viral prevalence
- Greater genetic diversity
- Ancestor or ancient lineages of “modern” mammalian viruses
- Carries more viruses per species of bat

LETTER

Host and viral traits predict zoonotic spillover from mammals

Kevin J. Oliva¹, Parvaz R. Hosseini², Carlos Zambrana-Torreal³, Noam Rosal⁴, Tiffany L. Beggs⁵ & Peter Daszak⁶

range—which may reflect human–wildlife contact. We demonstrate that bats harbour a significantly higher proportion of zoonotic viruses than all other mammalian orders. We also identify the

we conducted a comprehensive analysis of mammalian host–virus relationships and show that both the total number of viruses that infect a given species and the proportion likely to be zoonotic are predictable. After controlling for research effort, the proportion of zoonotic viruses per species is predicted by phylogenetic relatedness to humans, host taxonomy and human population within a species range—which may reflect human–wildlife contact. We demonstrate that bats harbour a significantly higher proportion of zoonotic viruses than all other mammalian orders. We also identify the taxonomic and geographic regions with the largest estimated number of ‘missing viruses’ and ‘missing mammals’ and therefore of highest value for future surveillance. We then show that phylogenetic host breadth and other viral traits are significant predictors of zoonotic potential, providing a novel framework to assess if a newly discovered mammalian virus could infect people.



Science

The study is “important for anyone interested in zoonotic spillover events,” says Linda Wang, who heads the “bat pack,” a research team in the Emerging Infectious Diseases Programme at the Duke-NUS Medical School in Singapore. Wang has spent many years arguing whether bats are special with Daszak, and says it’s exciting that the new paper comes from his group. **Daszak, meanwhile, is gracious in defeat: “Linda was right all along,” he says.**

Just what makes bats special is still unclear: there are many competing hypotheses, from a primitive immune system to echolocation creating droplet clouds that help spread viruses. **The next debate is about to take off.**



Researchers take blood from an American masked fruit bat in the Republic of the Congo, which are suspected of carrying the Ebola virus.

Bats really do harbor more dangerous viruses than other species

By Kai Kupferschmidt | Jan. 25, 2017 | 1:00 PM

What makes bats special?

Bat facts during flight

- Metabolic rate: 15-30x of resting rate
- Heart beat: ≥ 1,000 bpm
- Body temperature: 38-42 degrees C



Comparative Analysis of Bat Genomes Provides Insight Into the Evolution of Flight and Immunity
Guojie Zhang et al.
Science 339, 456 (2013);
DOI: 10.1126/science.1230835

Black flying fox (*Pteropus alecto*)



Strong positive selection on key innate defense pathways

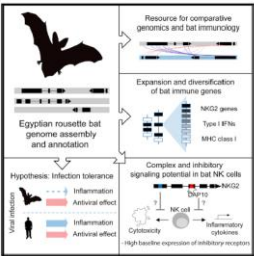
- 1) Enhanced DNA damage repair
- 2) Reduced inflammation



Article

The Egyptian Roussette Genome Reveals Unexpected Features of Bat Antiviral Immunity

Graphical Abstract



Authors

Stephanie S. Pavlovich, Sean P. Lovett, Galina Koroleva, ..., Mariano Sanchez-Lockhart, Thomas B. Kepler, Gustavo Palacios

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In Brief

The genome of the Egyptian fruit bat reveals how its immune defenses allow tolerance of pathogenic viruses.

May 2018

Immunity Previews

1076 Immunity 48, June 19, 2018

Holy Immune Balance, Batman!

Haley E. Randolph^{1,2} and Luis B. Barreiro^{2,3,*}

¹Department of Biochemistry, Faculty of Medicine, Université de Montréal, QC H3T 1J4, Canada

²Department of Genetics, CHU Sainte-Justine Research Center, Montreal, QC H3T 1C5, Canada

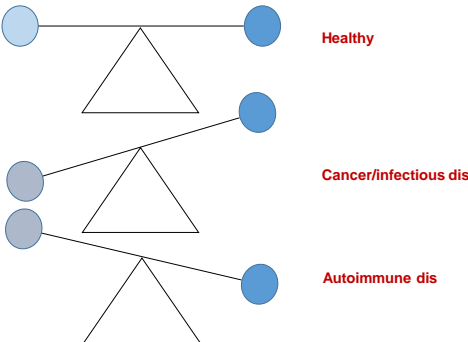
³Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, QC H3T 1C5, Canada

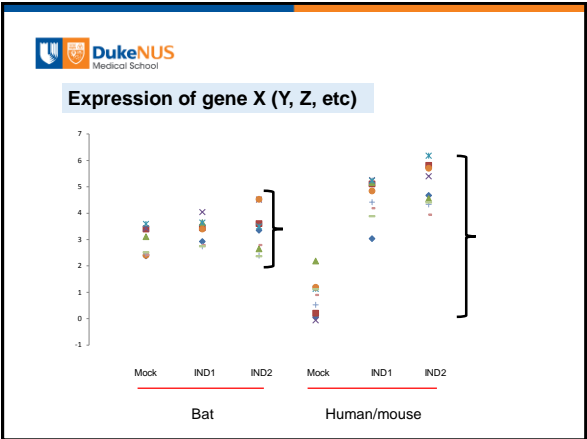
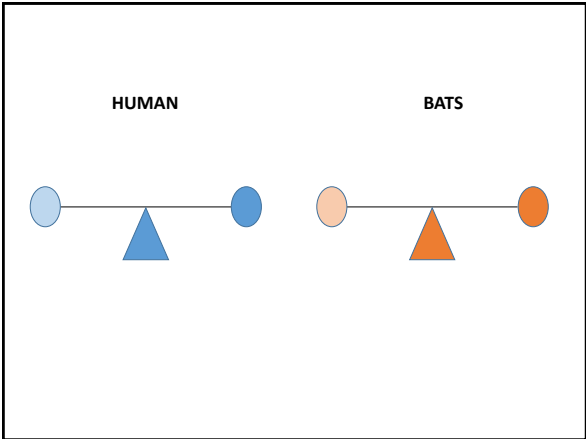
*Correspondence: luis.barreiro@umontreal.ca

<https://doi.org/10.1016/j.immuni.2018.05.016>

Bats are reservoir hosts of numerous viruses that cause severe pathology in humans. How bats cope with such pathogens remains elusive. In a recent issue of *Cell*, Pavlovich et al. (2018) describe several key adaptations in innate immune-related genes that suggest that the Egyptian roussette fruit bat relies on immune tolerance mechanisms to manage viral infections.

Innate defense/tolerance balance





DukeNUS Medical School

Published/unpublished findings

- More efficient DNA damage repair system
- Higher base level IFN α gene expression in some bat
- Higher base level expression of HSPs
- Higher base level expression of surface efflux pump proteins (ABC transporters)

- Missing AIM2-mediated inflammasome signaling
- Dampened NLRP3-mediated inflammasome activation
- Dampened STING activation
- Apparent lack of GvHD in bat mice

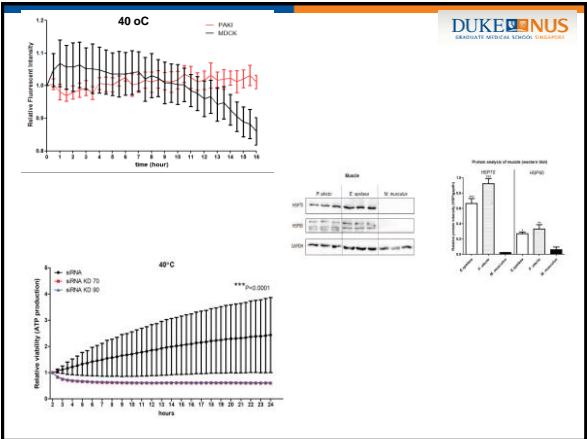
DukeNUS Medical School

Published/unpublished findings

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- ...

DukeNUS Medical School

Expression profile of heat shock proteins (HSPs) in bats



- Successful viral evolution hinges on the efficient sampling of mutated protein sequences.
- Often, these mutations are destabilizing to the proteins in which they occur.
- It is unknown how viral evolutionary capacity is influenced by the composition and activities of the host cell's protein homeostasis network.
- **Hypothesis:** viruses hijack the host cell's protein-folding machinery to help fold their own proteins and will therefore be better able to accumulate destabilizing mutations when more host chaperones are present.
- Early results suggest that influenza evolution is influenced by the host's protein-folding environment (modulated by HSP expression).

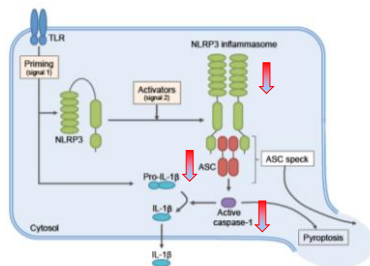
Hyper-folding ← Normal → Hypo-folding

Strong evolutionary pressure for dampened inflammation

Protective VS Pathogenic

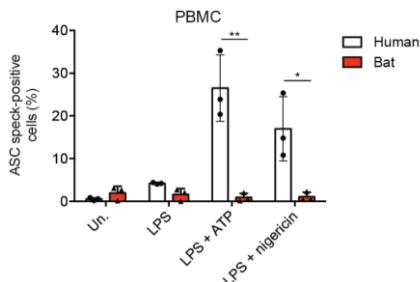
Inflammation & Diseases

Aging
Alzheimer
Arthritis
Autoimmune dis.
Cancer
Cardiovascular dis.
Diabetes
Eye dis.
Infectious dis.
Metabolic dis.
Pulmonary dis.
Neurological dis.

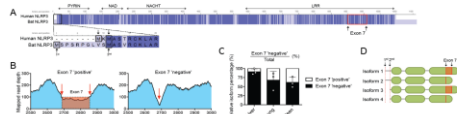


Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host

Matae Ahn¹, Danielle E. Anderson¹, Qian Zhang^{1,2,3}, Chee Wah Tan¹, Beng Lee Lim¹, Katarina Luko¹, Ming Wen¹, Wan Ni Chia¹, Shailendra Mani¹, Loo Chien Wang¹, Justin Han Jia Ng¹, Radoslaw M. Sobota^{1,4,5}, Charles-Antoine Dutertre^{1,6}, Florent Ginhoux^{1,6}, Zheng-Li Shi^{1,7}, Aaron T. Irving^{1,8} and Lin-Fa Wang^{1,8}



Dampening at both priming and activation stages



A bat-unique "exon 7-less" NLRP3 splicing variant

