

## PERSPECTIVE

# Bat and virus

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**Bat, the only flying mammal and count more than 20% of the extant mammals on earth, were recently identified as a natural reservoir of emerging and reemerging infectious pathogens. Astonishing amount (more than 70) and genetic diversity of viruses isolated from the bat have been identified in different populations throughout the world. Many studies focus on bat viruses that caused severe domestic and human diseases. However, many viruses were found in apparently healthy bats, suggesting that bats may have a specific immune system or antiviral activity against virus infections. Therefore, basic researches for bat immunology and virus-host interactions are important for understanding bat-derived infectious diseases.**

Bats, originated about 50 million years ago, are currently widely distributed and make up more than 20% of extant mammals on earth (Simmons, 2005; Teeling et al., 2005). Bats are traditionally grouped into two suborders: Megachiroptera (Megabat), which contains a single family *Pteropodidae* (42 genera, including 166 species), and Microchiroptera (Microbat), which contains 16 bat families (135 genera, including 759 species) within the order Chiroptera (Simmons, 2005). Megabat mainly feed on fruit, and some bats, such as *Pteropus*, have long distance migration capability. Most microbats feed on insects, while some feed on birds, lizards, frogs, fish or blood (vampire bat) (Aguirre et al., 2003; Patterson et al., 2003). Bats have various habitats, including caves, trees, roof and discarded tunnels, with a large group from hundreds to thousands of individuals in the same habitat. Because of many unique biological properties such as echolocation, hibernation, flying ability and living environment, bats are considered as enigmatic mammals.

### **BATS ARE NATURAL RESERVOIRS OF EMERGING AND REEMERGING HUMAN VIRUSES**

Bats as reservoirs of human viruses were recognized as early as 1920s when rabies was found in bat in South and Central

America (Sulkin and Allen, 1974), but bats as carriers of emerging zoonotic viruses were not well acknowledged until the mid-1990s. The number of identified bat viruses rapidly increased after the discovery of henipavirus and severe acute respiratory syndrome coronavirus (SARS-CoV). Up to today, more than 80 viruses, including members from families of *Rhabdoviridae*, *Orthomyxoviridae*, *Paramyxoviridae*, *Coronaviridae*, *Togaviridae*, *Flaviviridae*, *Bunyaviridae*, *Reoviridae*, *Arenaviridae*, *Herpesviridae*, *Picornaviridae*, *Hepesviridae* and *Adenoviridae*, have been isolated from different bat species (Calisher et al., 2006).

**Rabies virus** Since the discovery of bat borne rabies virus in 1920s, different genotypes of rabies or rabies-related viruses within the genus *Lyssavirus* of the family *Rhabdoviridae* have been documented in bats. There are seven recognized genotypes of lyssavirus (Bourhy et al., 1993): rabies virus (genotype 1), Lagos bat virus (genotype 2), Mokola virus (genotype 3), Duvenhage virus (genotype 4), European bat lyssavirus type 1 (EBLV-1; genotype 5), European bat lyssavirus type 2 (EBLV-2; genotype 6), and Australian bat lyssavirus (genotype 7). All the genotypes except Mokola virus have bat reservoirs (Badrane and Tordo, 2001). Human rabies caused by bat lyssavirus was incessantly reported in South and North America, Europe, Australia and Africa (Hanna et al., 2000; Favi et al., 2002; Badilla et al., 2003; Fooks et al., 2003; Nathwani et al., 2003; Paweska et al., 2006; Blanton et al., 2008; van Thiel et al., 2008).

**Henipavirus** The *henipavirus* is a new genus with the family *Paramyxoviridae* and contains only two closely related but distinct members, hendra virus (HeV) and nipah virus (NiV) (Eaton et al., 2007). Restricted only to Australia, HeV was initially described after an outbreak of severe respiratory disease in horses during September 1994, which ultimately results in deaths of 13 horses and 1 horse trainer in Hendra, Australia, a suburb of Brisbane (Murray et al., 1995). Since then, several sporadic outbreaks have been reported in Australia in 1999, 2004, 2006–2008 (Field, 2008). NiV was

discovered in Malaysia during a major outbreak of acute respiratory syndrome in pigs occurring from September 1998 to June 1999, resulting in 265 cases of encephalitis in humans and 105 deaths (Chua et al., 2000). The similar disease outbreak has also been documented in Singapore, India in 2001, Bangladesh in 2001–2008 (Paton et al., 1999; Chadha et al., 2006; Eaton et al., 2006).

Serologic and virologic studies suggest that bats are the principle reservoir hosts of henipaviruses. Numerous frugivorous bat species of the genus *Pteropus* (family *Pteropodidae*) exhibit a high seroprevalence for henipaviruses. In addition, HeV has been isolated from *P. poliocephalus* and *P. alecto* in Australia (Halpin et al., 1999), NiV has been isolated from *P. hypomelanu* in Malaysia (Chua et al., 2002) and *P. lylei* in Cambodia (Reynes et al., 2005). Antibodies to henipavirus have also been detected among both frugivorous and insectivorous bats in Thailand (Wacharapluesadee et al., 2005), Indonesia (Sendow et al., 2006), Madagascar (Lehle et al., 2007) and China (Li et al., 2008); however, no virus has been isolated from those tested bat samples.



**SARS-CoV** Bats are recently identified as natural reservoir of SARS-CoV that caused outbreaks of human respiratory disease during 2002–2003 in China and resulted in 8422 cases with 916 deaths in 29 countries and regions (Chan-Yeung and Xu, 2003). Antibody and genomic sequences similar to SARS-CoV were discovered in *Rhinolophus* bat, including *R. sinicus*, *R. pearsoni*, *R. macrotis* and *R. ferrumequinum* and *R. pusillus* (Lau et al., 2005; Poon et al., 2005; Ren et al., 2006). The nucleotide sequences of bat SARS-like CoVs (SL-CoV) have 78%–92% identities to SARS-CoV and among themselves, and display great genetic diversity. The phylogenetic analysis indicated that *Rhinolophus* bat may carry the direct progenitor of human SARS-CoV (Hon et al., 2008).

**Filoviruses** Marburg virus and Ebola virus, belonging to the family *Filoviridae*, are two emerging viruses that cause human hemorrhagic fever disease (HF) (Sanchez et al., 2007). The

Marburg virus was recognized during 2-center outbreaks in Marburg, Germany, and Belgrade, former Yugoslavia, in 1967 (Malherbe and Strickland-Cholmley, 1968). The disease was associated with laboratory work using African green monkeys (*Cercopithecus aethiops*) imported from Uganda. Subsequently, outbreaks and sporadic cases have been reported in Angola, Democratic Republic of the Congo, Kenya, South Africa (in a person traveled to Zimbabwe) and Uganda (<http://www.who.int/csr/disease/marburg/en/>). The Ebola virus was first identified in a western equatorial province of Sudan and in a nearby region of Zaïre (now the Democratic Republic of the Congo) in 1976 after significant epidemics in Yambuku in northern Democratic Republic of the Congo, and in Nzara in southern Sudan (Emond et al., 1977). Since then, numerous outbreaks have been documented in Democratic Republic of the Congo, Uganda and Sudan (<http://www.who.int/csr/disease/ebola/en/>). Four different Ebola virus strains were identified: *Zaire*, *Sudan*, *Reston* and *Côte d'Ivoire* (Ivory Coast) ebolaviruses, and the former two are associated with HF outbreaks in Africa with high case fatality (53%–90%) (Sanchez et al., 2007).

Both *Zaire* and *Sudan* strains have been detected in bats. Marburg virus was detected in fruit bat *Rousettus aegyptiacus* in Gabon, Uganda and Democratic Republic of the Congo and in insectivorous bat *Rhinolophus eloquens* (Swanepoel et al., 2007; Towner et al., 2007, 2009). Zaire Ebola virus was detected in 3 bat species (*Epomops franqueti*, *Hypsignathus monstrosus*, and *Myonycteris torquata*) in Gabon and the Republic of the Congo (Leroy et al., 2005; Biek et al., 2006; Gonzalez et al., 2007; Pourrut et al., 2007, 2009). The available sequence data demonstrated that both Ebola and Marburg virus in bats display genetic diversity.

**Melaka virus** The Melaka virus, a novel reovirus, was isolated from a 39-year-old male patient in Melaka, Malaysia, who was suffering from high fever and acute respiratory disease upon virus isolation. Two of his family members developed similar symptoms approximately 1 week later and had serological evidence of infection with the same virus. Epidemiological tracing revealed that the family was exposed to a bat in the house approximately 1 week before the onset of the father's clinical symptoms. Genome sequence analysis indicated a close genetic relationship between Melaka virus and Pulau virus, which is a also reovirus isolated in 1999 from fruit bats in Tioman Island, Malaysia (Chua et al., 2007).

## PERSISTENT INFECTION AND GENETIC DIVERSITY OF BAT VIRUSES

In addition to bat borne virus that caused severe human diseases, many other bat viruses that has no evidence to cause animal or human diseases have been discovered in bat populations throughout the world. These viruses were regularly detected in apparently healthy bats and display genetic diversity.

**Other Bat CoVs** During the search for the origin of SARS-CoV, numerous novel CoVs were detected in large numbers of bat species in China, South and North America, Germany and Africa (Poon et al., 2005; Chu et al., 2006; Ren et al., 2006; Tang et al., 2006; Dominguez et al., 2007; Lau et al., 2007; Muller et al., 2007; Woo et al., 2007; Carrington et al., 2008; Gloza-Rausch et al., 2008; Misra et al., 2009; Pfeffler et al., 2009). The phylogenetic analysis based on the fully sequenced Bat-CoV indicated high genetic diversity that of bat CoVs, which were grouped into CoV group 1, group 2a, 2c and 2d (Ren et al., 2006; Tang et al., 2006; Woo et al., 2007; Lau et al., 2007).

**Bat Astroviruses** A group of novel astroviruses was found in apparently healthy insectivorous bats, particularly in the genera *Miniopterus* and *Myotis* (36%–100% and 50%–70%, respectively), in Hong Kong (Chu et al., 2008). Similar viruses were detected in a large numbers of bat samples in mainland China (Zhu et al., 2009). The phylogenetic analysis revealed a remarkably high genetic diversity of bat astroviruses that form five monophyletic groups clustered in the genus *Mamastrovirus* within the family *Astroviridae*. Some bat astroviruses may be phylogenetically related to human astroviruses, implying potential risk of inter-species transmission of *Mamastrovirus*.

**Herpesvirus** Herpesvirus was initially discovered in little brown bats (*Myotis lucifugus*) by virus morphology (Tandler, 1996) and later detected in different bat species in The Philippines, Africa and Europe with molecular detection methods (Wibbelt et al., 2007; Molnar et al., 2008; Razafindratsimandresy et al., 2009; Watanabe et al., 2009). The phylogenetic analysis based on obtained partial gene sequences indicated that bat herpesviruses display genetic diversity and form distinct clade within the subfamily *Alphaherpesvirinae*, *Betaherpesvirinae* and *Gammaherpesvirinae*.

**Adenovirus** A novel adenovirus was isolated by a Japanese scientist during tissue cultures derived from bat spleen from fruit bat *P. dasymallus yayeyamae*. The partial polymerase sequence of this bat adenovirus showed homolog to tree shrew adenovirus 1 (70% amino acid sequence identity). A Germany group later reported another novel adenovirus in German bats (Sonntag et al., 2009). Recently, our group has also detected genetic diversity adenoviruses in 5 bat species in China (unpublished results), indicating a wide distribution of adenovirus in bat populations.

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### Future screening and preparation of diagnostic methods of bat viruses

Bats viruses did not attract human attention until recent years when several emerging and reemerging human viruses were

associated with bats. However, information about the natural history of most viruses in bats is limited. It is evident that most of the bat viruses have existed in bats for long time. Why did some of them cause severe disease in domestic animals and human in recent years? The invasion of bat habitats and expanding agricultural industry increase the close contact opportunity between bats and human, thus increase the opportunity of virus transmission from bat to domestic animals and human. The molecular detection technology significantly contributes to the discovery of more bat viruses. Considering the diversity of bat species in the world, the currently identified bat viruses may represent only a small part of bat reservoir. Therefore, a wide-ranged screening of bat viruses is required to prepare specific diagnostic methods for preventing future emerging viral diseases in animals and human.

### Studies of virus interspecies transmission and evaluation of potential risk of bat viruses

Viruses usually have narrow host ranges, which restrict them transmitted from one animal to others. However, zoonotic viral diseases consist of more than 70% among the emerging and reemerging viral diseases (Jones et al., 2008). The first step for successful interspecies transmission is that the virus can use the same receptor as found in their original host of other animals for their entering the invading host cells. Some bat borne viruses, such as henipaviruses, have wide host ranges and can easily transmit from bats to animal and human as their cellular receptor ephrin B2 and B3 are highly conserved in different animals. This may explain why Hendra virus and Nipah virus continually revisiting human and caused disease outbreaks in recent years. Unlike henipaviruses, SARS-CoV, which use the angiotensin converting enzyme 2 (ACE2) as cellular receptor, has a relatively narrow host ranges. The ACE2 protein of different origins are variable at the N-terminal ends that contact directly the receptor binding domain (RBD) of the SARS-CoV spike protein (S). A minor amino acid change in the RBD or ACE2 N-terminal end can abolish the entry of SARS-CoV (Li et al., 2005; Ren et al., 2008). This may partially explain why SARS-CoV completely disappeared when the transmission chain (civet and other small mammals as intermediate hosts) was interrupted. Thus, further studies should focus on the interspecies transmission of bat viruses and evaluate the potential risk of bat viruses to domestic animals and human.

### Bat immune response on virus infections

Most bat viruses known today were discovered in apparently healthy bats. Experimental infection to bat by henipavirus virus and rabies virus also demonstrated that bat shed the virus but did not produce any clinical syndrome as did in other animals and human (Almeida et al., 2005; Hughes et al., 2006; Tjornehoj et al., 2006; Middleton et al., 2007), suggesting that bats may have specific immune system or

antiviral activity against virus infections. Further knowledge of immune response of bats against viruses might shed light on some key questions of the bat-derived virus infectious diseases. It will be necessary to determine bat genome or transcriptome, to establish bat cell culture-based assays and bat-specific reagents to examine lymphocyte proliferation, antibody and cytokine synthesis, cell-mediated immune responses, and to develop a host of other immunologic functions in bats.

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