The interplay between viruses and the immune system of bats

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Bats are an abundant and diverse group of mammals with an array of unique characteristics, including their well-known roles as natural reservoirs for a variety of viruses. These include the deadly zoonotic paramyxoviruses; Hendra (HeV) and Nipah (NiV)[1,2], lyssaviruses[3], coronaviruses such as severe acute respiratory coronavirus (SARS-CoV)[4] and filoviruses such as Marburg[5]. Although these viruses are highly pathogenic in other species, including humans, bats rarely show clinical signs of disease whilst maintaining the ability to transmit virus to susceptible vertebrate hosts. In addition, bats are capable of clearing experimental infections with henipaviruses, filoviruses and lyssaviruses at doses of infection that are lethal in other mammals[6–12]. Curiously, the ability of bats to tolerate viral infections does not appear to extend to extracellular pathogens such as bacteria, fungi and parasites[13]. Over the past few years, considerable headway has been made into elucidating the mechanisms responsible for the ability of bats to control viral replication, with evidence for unique differences in the innate immune responses of bats[14–20]. However, many questions remain around mechanisms responsible for the ability of bats to co-exist with viruses, including their ability to tolerate constitutive immune activation, the triggers associated with viral spillover events and the sites of viral replication. Although bats appear to have all of the major components of the immune system present in other species, their unique ecological characteristics (including flight, high density populations and migration) combined with their long co-evolutionary history with viruses has likely shaped their immune response resulting in an equilibrium between the host and its pathogens.

The availability of bat genome and transcriptome datasets from a number of bat species has accelerated the identification of key components of the immune system[17,19,21–25]. These studies have also provided evidence for a link between flight and immunity with the inadvertent selection on key immune genes and pathways as a consequence of the evolution of flight[19]. Functional studies *in vitro* have demonstrated that differences in the innate immune system of bats play a key role in controlling viral replication. In particular, components of the interferon (IFN) system, including IFN-alpha (IFNα), IFN signalling molecules and IFN stimulated genes are constitutively expressed in unstimulated pteropid bat tissues and cells[15,17]. Although the IFN system provides the first line of defence against infection, bats are the only species known that constitutively activate their IFN response in the absence of infection, providing evidence that the baseline activation of the innate immune system of bats is considerably higher than that of other mammals. Presumably, the constitutive expression of IFN allows bats to avoid the lag time between infection and immune activation, thus providing a more immediate response. However, prolonged exposure to IFN is generally associated with pathological side effects in other species[26]. Elucidating how bats maintain IFNα expression in the absence of inflammation could therefore have important implications for treating viral infections in humans and other species. Clearly, much remains to be learned about the unique innate immune response of bats.

Much of what we know about the kinetics of the immune response of bats to viruses *in vivo* has been obtained from experimental infections. With the exception of rabies and lyssavirus infections, these experiments have demonstrated that bats rapidly clear infection with no clinical disease[6–9,11,12,27,28]. Experimental infections

Figure 1. Captive *Pteropus alecto*. (Photo courtesy of Susanne Wilson, CSIRO.)

of bats with the henipaviruses; HeV and NiV have provided the most information to date regarding the kinetics of infection. Pteropid bats (Figure 1) infected with henipaviruses have detectible viral RNA in rectal and throat swabs from 2–7 days post infection (dpi) and in urine and blood samples collected after 7 dpi[8]. However, viremia is typically short and viral antigen is generally undetectable in tissues by 21 dpi[8,11]. Although antibody responses have been the only immune parameter measured (due partly to the lack of bat specific reagents) these studies have provided important evidence for the ability of bats to rapidly clear viral infections. Virus specific antibodies have been detected in wild caught bats indicating that they are capable of generating an antibody response[29–33]. However, evidence from experimental infections have shown the development of neutralising antibodies is often delayed and some animals fail to generate an antibody response within the timeframe of the experiment[8,11,12,27,28]. This coupled with the constitutive activation of components of the innate immune system may mean that the adaptive immune response in bats is less critical. Much less is known about T cell mediated immunity in bats and no studies have examined T cell responses in experimentally infected bats. However, differences in the repertoire of major histocompatibility complex (MHC) class I molecules and the self and HeV peptides they present already point to differences in T cell mediated responses to infection[34,35]. Thus, like the innate immune response, the cell mediated response may also have undergone changes associated with the long co-evolutionary history of bats with viruses.

The fine balance between the immune system of bats and their viruses has presumably achieved an equilibrium that is able to support both the survival of the host and low level replication of the pathogen. Despite the seemingly high activation of the bat's innate immune system, viruses have been isolated from naturally infected wild caught bats and spillover of viruses from bats to other susceptible species on an ongoing basis[3,4,36–38]. Thus, viruses appear to be constantly circulating in bat populations at some level, either as a consequence of ongoing infections of naïve individuals, through oscillating herd immunity or though episodic shedding from persistently infected individuals[39]. Natural cycles driven by environmental (e.g. climate, food availability, human activity) and internal triggers (e.g. mating, birthing, lactation) have been hypothesised to dampen the bat's immune response, leading to increased viral replication and consequently to increased spillover events[39–41]. However, evidence to link specific physiological or ecological triggers with changes in immune responses and viral replication is currently lacking and considerable work is still required to fully understand the relationship between viruses and the ability of the immune response of bats to control replication. This information will lead to new insights for the prediction and prevention of spillover events and for the treatment of infectious diseases in humans and other species.

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Biographies

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