Genetic Adaptations in Bats for Spreading Zoonotic Diseases

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Abstract

Zoonotic disease, or zoonoses, are viral disease that can spread across different species. Various mammals, such as rodents, primates, birds, or livestock, develop and spread zoonoses to humans. The zoonoses spread from bats to humans are often particularly contagious and lethal. Many studies have pointed to how traits like immune genes and flight mechanisms in bats have evolved to contain additional adaptations, making them a perfect genetic host in which zoonotic viruses evolve. Since bats have such strong immune responses while exhibiting no symptoms, viruses hosted by bats have more time to evolve rigorously before they are transferred to humans. With the increase in human population, habitat loss and climate change force bats to live in closer contact with us, allowing such diseases to spread far and rapidly in the human population. Two completely different bat species can independently give rise to the same virus within several months, showing the drastic co-evolutionary relationship bats have with encouraging viral growth. This paper explores how bats have evolved to become excellent reservoirs and spreaders for zoonotic viruses to humans due to adaptations in genetic immunities and evolved behavioral patterns across different species of bats. As bats evolve to have more immune response mechanisms for their survival, viruses harbored by them are given time to develop resistance and adapt into new forms.

Introduction/ Background

Some of the most popular known disease outbreaks, such as SARS-1, the Ebola Virus in West Africa, the spread of Nipah viruses in Southeast Asia and Austraila, all either started from or are now having a leading source from bats. For example, in Latin America, rabies is caught in more cases now by contact with bats than by contact with dogs, which used to be the biggest cause (Chomel et al. 2014). Diseases such as these evolve at such a scale that they turn into epidemics, plagues, or widespread pandemics. Bat-hosted viruses are a hot topic among ecological and health scientists, yet can only truly be targeted when understood in detail, such as understanding which elements of the genetic evolution of bats ~~that~~ has allowed for the extensive mutation of viruses they carry. The bat's immune genes allow for such a wide range of variations to the virus it hosts that it is inevitable that such viruses end up becoming transferable to a wide variety of mammals, and, both direct and indirectly, to humans.

The strain of bats' shrinking environments causes the need to migrate more, exposing various bat populations to more sources of viral disease but also to more hosts to spread it to. The bats who die off from viruses eliminate those viruses in them, and so the bats with the strongest immune responses survive the most due to natural selection along with the viruses that those bats harbor. This preserves the viruses in which the bats with the strongest immune system hosted, which in turn, means the most adapted viruses end up surviving.

Bats have a heavy-equipped immune system, due to a series of evolutionary advances over the span of 50 million years. Unlike humans and most mammals, bats are asymptomatic, meaning they don't exhibit any symptoms or inflammation when infected with a virus. With this trait, they don't die from a virus, but remain carriers for it once contracted.

A lot of evolutionary details on bats are unknown, and so when traits are discussed in this paper such as flight, migration, the undergoing torpor or other behavioral traits, it is assumed that these traits have already evolved in bats over millions of years. When discussing evolutionary traits of immune responses, however, the focus is on the genetic adaptations for immune defenses that may have evolved over millions of years, can change from year to year, or simply change from one generation to another in a given study.

How viruses advance in bats so well

Although bats vary in abilities, size and shape around the world, they share a role as especially efficient vectors and growing grounds for viral disease all over the globe. A study surveying hepadnaviruses in bats from different areas in China showed that many diversified strains related to previous viruses specific to bats in one province of China had developed in modern bats across 2 other provinces. A new virus was also found in these bats, which was closely related to a hepadnavirus from bats in West Africa, which lived in a completely different type of environment and looked completely different, being a species far and isolated from the China bats. Not only did this confirm that the hepadnaviruses had been co-evolving with bats for a long time in history, but it also proves how easy it is to infect across species of bats from one species in a particular biome to another. (Nie et al. 2017). So, it is no wonder how viruses from bats often spread like wildfire into epidemical scales, since they can spread between species and across the world easily, as these two independent species of bats ended up developing the same strain of virus independently, and only over the course of one study.

A similar study in Spain identified and coded the entire genome of five picornaviruses, and one new subspecies of the virus in various species of bats. Calhevirus was also found, which is a virus usually found in bats from distant lands across the Iberian peninsula. These findings

show us a snapshot of how globally spreadable the bats' viral diseases are especially once allowed to mutate within a bat's system (Carrascosa et al. 2024), as well as the potential of just one species to produce a large scope of disease types.

How bats easily spread viruses

The behavioral nature of bats is strained as they continue to lose their habitat to humans. Their particular needs and behaviors make it difficult to adapt to these changes. Bats have seasonal habits that vary depending on the geological area they inhibit, which means they have particular periods and locations in which they mate, give birth, migrate, and undergo a sort of hibernation called torpor (Hayman et al. 2012). All these aspects will change the population density, contact amount between bats in a colony, and immunity strength of the bats in a given population. As human civilization continues to develop, bats and humans are in closer proximity for space and greater overlap of resources. So, changes to their natural rhythm of life are a sure way for viruses to be contracted and spread throughout dense, stressed populations. Thus, the more humans interrupt bats' habitats and behavioral patterns, the more stress is put on the bats, and therefore more viruses they are susceptible to and eventually suscept us to.

The main routes that cause strain on bats are deforestation, urbanization, agricultural expansion, and mining, since these all fragment or destroy common bat habitats. One example is the Hendra virus in Australia spread to horses, dogs and humans, and had a 70% fatality rate. This disease was found to spread from horses going under trees where bats drop their waste, then to dogs and humans that live in close proximity. The Menangle virus in Wales came from Flying foxes which spread to pigs, over to pig farmers causing human still births. In addition, Marburg viruses were found in miners who worked in bat-inhabited caves, as well as coronavirus proteins found in bat droppings where guano miners worked (Chomel et al. 2014).

Figure 1 summarizes the spread of Nipah viruses in Australasia over the course of 30 years and how the virus became increasingly communicable as well as fatal while it spread to neighboring countries. This ties together the concepts of how rapidly bat zoonoses evolve to become more resistant and harmful as well as how rapidly they spread to other species and across different countries and oceans.

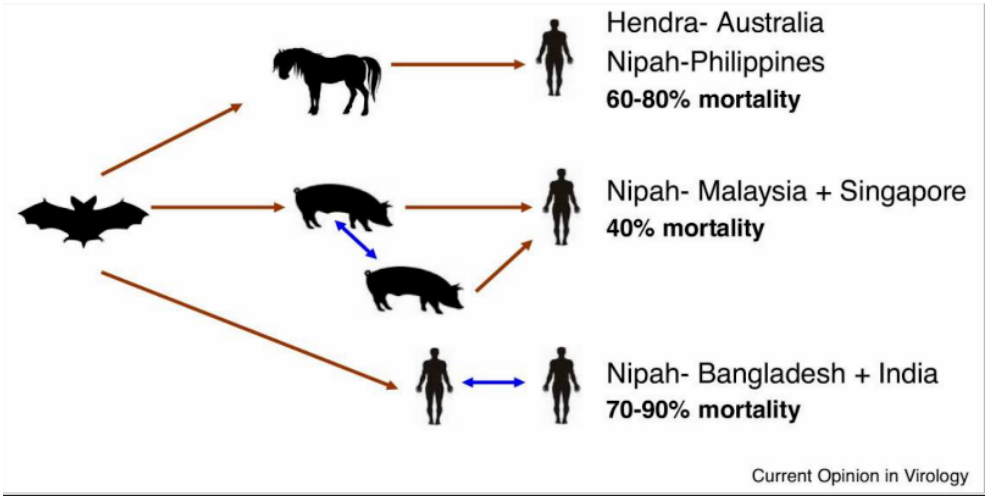

Figure 1: *The spread of bat zoonoses in Australasian areas through other closely-living mammals to humans, and the level of fatality in each area (Wang and Anderson 2019)*

In a detailed observation, bats spend much of their lifetime flying, whether it be during migration or while hunting or scavenging for food. While in flight, a bat's metabolism is increased, which can produce byproducts that usually damage an organism's cells and shorten their life. However, despite these odds, bats tend to have healthier cells and a long lifespan in comparison to other animals in flight. Their metabolic rate specifically, a 15-fold rate compared to a two-fold rate found in other flying species This high metabolic rate is thought to mimic the responses in our bodies when we have a fever, which helps the immune responses to predict how a virus might mutate in one's body. This is known as the ''flight as fever'' hypothesis, which assumes that this increased metabolism in a bat, even though it should actually make a bat

weaker, can allow for viruses to live in them without making them sick because of the fever-like responses that a bat's flight triggers. This response acts as a preventative measure toward viruses while the virus's presence is small, rather than a full immune response happening after a viral outbreak in the body occurs. (Gupta et al. 2021).

Unique Adaptations in the Bat Genome

Bats have a highly evolved immune system. To begin, they have a large amount of B-cells in their immune system, as well as antibodies, to viruses such as Hendra, Nipah, Marburg, Ebola, and West Nile viruses (Liu et al. 2023). But how are all of these immunities and anti-bodies contained in the first place? Deciphering the genome of bats may give us more information. A bat's genome not only has a collection of long-established immunity codes over millions of years, but also evolves quickly to fight new viral genes (Liu et al. 2024). In a study looking at fibroblast cells for immunity gene transcription responses, immunity genes in rousettus and pipistrellus bats showed evidence of divergent immune genes that were not found to be present in humans, primates, rats, nor mice (refer to figure 2).

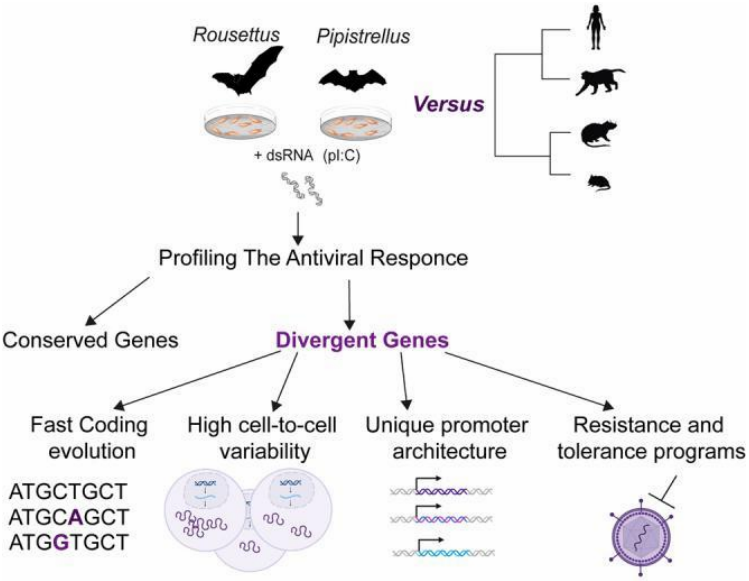

Figure 2: *Fibroblast tissue of two bat species were grown in a petri dish and exposed to viral RNA to activate immune genes, then observed for divergent genes (Schneor et al. 2023).*

These findings included a high variance in immune genes between cells, which indicates a fast adaptation rate to new viruses. Another characteristic in their immune genes was unique promoter sequences, which prevent overexpression and autoimmune reactions. This also allows for a fast-acting expression of that antiviral gene once the specific virus is properly identified by a receptor. Genes that allow for more viral tolerance and resistance genes were also found, as well as resistance and tolerance programs. Programs as these are defined as sets of codes for genetic and molecular immune processes that are activated in response to a pathogen, injury, or other immune challenge. These programs will regulate certain genes that encode proteins and molecules essential for recognizing threats, signaling immune responses, and executing defense mechanisms. In addition, immune programs are usually defined as having been established from millions of years of evolution. These are just a few examples of the extensive antiviral program encoded in a bat's DNA (Schneor et al. 2023).

Another study was conducted, in which the antiviral genome of black flying foxes was compared to the corresponding genome of humans. For flying foxes, their IRF7 gene, which is an immune response regulator, didn't have an activator, so it would be constantly running and fighting against a variety of viruses, and transfer immune information even in cells that weren't currently infected. Many viruses also inhibit the activators of IRF genes, so by not using a receptor, this gene wouldn't have to face that problem. In contrast, the IRF7 gene in humans had an activator, so it would need to be activated by interferon signaling in the case of a viral outbreak in the body. Furthermore, in bats, the C-terminal in the protein produced by this gene also had extra serines compared to that in humans, providing support to antiviral processes since

many enzymes that catalyze antiviral processes require serine proteases. (Riviera et al. 2024). Therefore, since humans do not have these genetic strengths against viral attacks, it is easy for viruses, when rooted from a bat's immune system, to be extra overwhelming to the human body's immune system, since it would have had to overcome the many evolutionary hurdles of a bat's antiviral responses before being spread to us.

Analysis and Conclusions

As stated before, bats exhibit adept immune responses, which allow them to host viruses that evolve rapidly, as exhibited in the spread of these viruses to humans and the incline of their severity. They have a long co-evolutionary history with many viruses, giving them an evolutionary library of immune programs as their defense. In addition to this long evolutionary history, bats possess immunity genes that allow for harbored viruses to mutate, advance, and develop resistance like no other while in their systems. They possess unique qualities such as "flight fever" responses that allow for viruses to stay in their bodies without them exhibiting symptoms, which allows such viruses to continue accumulating even more mutations.

With the decline of available habitats, the environmental strain on bats causes them to become efficient carriers for a variety of diseases. As human population and developments increase, this feedback loop is reinforced, putting more pressure on bats and also increasing human contact and spread of infection from vulnerable bats to relatively immune-deficient humans. These environmental factors are just the kick-starters of co-evolution of viruses in their chiropteran hosts, as they speed up the natural selection process. The virus that transfers to a human is the virus from the bats that survived and were the fittest, which means it's a virus that resisted the bats with the best immune defenses. This leads to diseases that, once spread to humans, cause lethal and intolerable symptoms.

Studies used in this paper were based on research methods such as metagenomic next-generation sequencing or MNGS (Chomel et al. 2014) to identify new RNA and DNA viruses in bats, as well as linear discriminant analysis or LDA (Baker et al. 2012) to ensure that the type of host of the virus being studied isn't from the bat's diet but actually a host that inhabits mammals. While most of these studies were fairly new, the inferences made need more data to find the big picture of whether spreading diseases is directly correlated to the unique immune responses in bats (Liu et al. 2024), so there are more reasons to be found, but from what we know about carriers for viruses and asymptomatic species, this is most likely the case.

There are many unknown details in which future research may help us to better maintain the environment for bats as well as understand the sparks that cause such wildfires of disease we catch from them. For example, if we were able to isolate bats in their "flight fever" metabolic mode, which triggers a proactive immune response, would we be exposed to new ways of predicting the uprising of new virus mutations and speed up the process of developing vaccines? One way in which future research could be applied is to identify the components of a bat's immune genes enough to one day perform recombinant DNA procedures to try to see if such attributes could be spliced and inserted into the genes in the cell of a similar mammal. Success in this could indicate new ways to produce antibodies, introduce immunities, or isolate dead viruses. Such findings could speed up the process for vaccine production, or even strengthen the immune tolerance in livestock and advance the efficiency of vaccines.

Individual communities should dedicate time to identifying hotspots of contact between bats and intermediate mammals through which diseases are spread to humans. Identifying these resources, such as barns, mining caves, or food sources shared with bats such as trees could help a community so that their local environmental management can provide alternative sites that are

safe for the bats to flourish while also keeping their communities safe from bats. Management can create action plans to reserve old barns as bat sanctuaries, construct caves, or plant wild fruit trees on a conservation site, as an attempt to compensate for the bat habitat demolition. In turn, these small actions can prevent the spread of disease through other wildlife, livestock, or human workers in such areas, by addressing the root of the problem. Such measures are relatively cheap, easily done, and resourceful, especially if old or run-down infrastructures like abandoned barns or caves are reserved for local bats and protected from the public.

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