Virology

Bats' genomic blueprint of viral tolerance

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Bats carry viral pathogens that typically do not lead to severe disease in the bats themselves but can be lethal to humans. Adaptations in certain immune genes might contribute to this resistance. **See p.449**

Bats are natural reservoirs for a wide range of viruses that can be lethal to humans, such as Ebola virus, Nipah virus and certain coronaviruses[1]. Despite carrying these pathogens, bats rarely develop disease – a phenomenon that has intrigued scientists for decades. On page 449, Morales *et al.*[2] provide insights into the genomic adaptations that enable bats to tolerate viral infections while remaining mostly unaffected by the harmful inflammation that the viruses cause in humans. The authors' findings reveal that evolutionary changes in specific immune-related genes underpin bats' extraordinary resilience.

To uncover the genomic basis of bats' resistance to viral diseases, the authors used long-read-sequencing and genome-assembly techniques to analyse ten bat species, with a focus on those known to harbour viruses that can be passed to humans. They then compared the genomes of 115 mammalian species (including the newly assembled bat genomes and those of 10 other bat species) and looked for evidence of positive selection, a process in which a genetic variant increases in frequency in a population because it is evolutionarily favourable.

They found that bats exhibited an exceptionally high rate of positive selection in certain immune genes involved in recognizing pathogens, regulating inflammation and responding to viruses. One of the genes that showed a particularly striking adaptation was *ISG15*. In humans, the ISG15 protein helps to combat viruses, but it also contributes[3,4] to destructive inflammation during severe cases of infections such as COVID-19.

ISG15's antiviral function is a consequence of its ability to bind to viral or host proteins inside vertebrate cells, in a process called ISG15 conjugation or 'ISGylation'. The protein can also exist in a free, non-conjugated form that can be secreted by cells into their surrounding environment, and it is this extracellular version of ISG15 that is associated with inflammation[4].

Morales *et al.* found that, in rhinolophid (horseshoe) and hipposiderid (Old World leaf-nosed) bats – which carry coronaviruses closely related to SARS-CoV-2 – the ISG15 protein is missing a cysteine amino-acid residue at position 78 (Cys78). Analyses of protein function revealed that, compared with versions of ISG15 that do have Cys78 (such as human ISG15), the Cys78-deleted ISG15 has an increased ability to conjugate to other intracellular proteins, and thus has stronger antiviral activity. Furthermore, the Cys78-deleted ISG15 bat protein was secreted from cells to a lesser extent than was human ISG15. The authors propose that these changes in ISG15 allow bats to effectively block viruses without triggering the excessive inflammation that is seen in humans (Fig. 1).

Bats are unique among mammals for their ability to fly, as well as for their exceptional longevity and echolocation[5]. Flight imposes intense metabolic demands, producing chemical by-products such as reactive oxygen species that can trigger inflammatory responses[6]. How bats counteract the potentially damaging inflammation that is driven by metabolic stress remains mostly unknown.

Morales *et al.* showed that adaptations in immune-related genes, rather than in genes linked with echolocation or longevity, can be traced back to a common ancestor that evolved powered flight. This finding suggests that there is a connection between bats' immune-system adaptations and their evolution of flight. One hypothesis is that these changes evolved to reduce the inflammation caused by flight-induced metabolic stress, and inadvertently enhanced bats' capacity to tolerate viral infections. This intricate interplay between the physiology of flight, metabolism and immunity underscores the evolutionary pressures that have shaped bats' resistance to viral diseases.

The study also highlights intriguing species-specific and virus-specific differences in bats' antiviral defences that cannot be explained by ISG15's known functions. For instance, although all rhinolophid and hipposiderid bats lack Cys78 in ISG15, the ability of these species to inhibit viruses still varies. This indicates that other immune functions that are specific to certain bat species are at play and

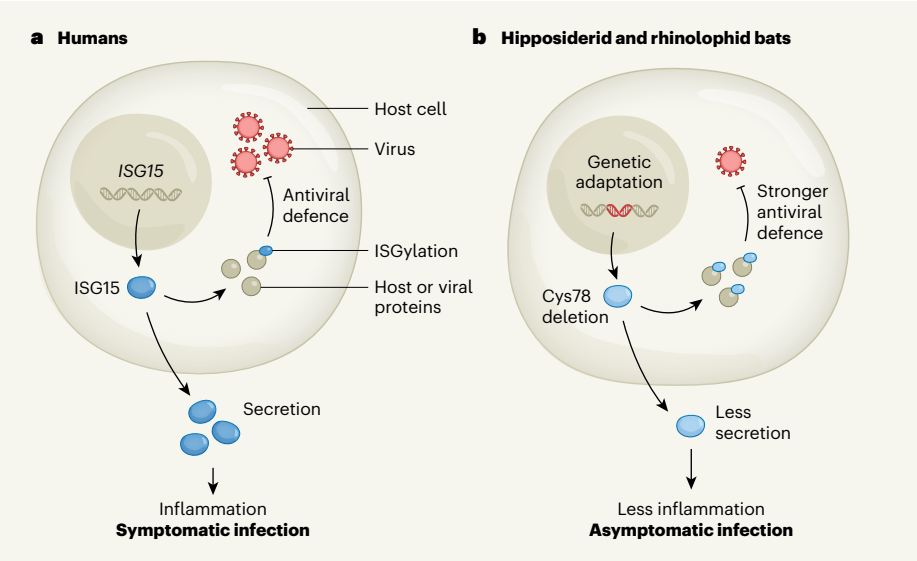

Figure 1 | Adaptations in immune genes underpin bats' defences against viruses. Bats are reservoirs for viruses that can cause severe disease in humans; however, the bats themselves are resistant to disease. Morales *et al.*[2] compared the genomes of 115 mammalian species, including 10 newly assembled bat genomes, and found evidence of positive selection (genetic changes that are evolutionarily favourable) in genes that encode immune-system proteins – including *ISG15*. **a**, In humans, ISG15 is added to proteins from either the host cell or the invading virus in a process called ISGylation, which contributes to antiviral defences. ISG15 is also secreted from cells, and extracellular ISG15 triggers inflammation that produces the symptoms associated with viral infection. **b**, ISG15 from rhinolophid (horseshoe) and hipposiderid (Old World leaf-nosed) bats lacks a cysteine amino-acid residue at position 78 (Cys78 deletion), which enhances ISGylation and leads to more effective antiviral defences, compared with human ISG15. Bat ISG15 is also secreted from cells less efficiently than is human ISG15, limiting the inflammation that causes symptoms.

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Greenland's ice is fracturing faster than expected

As glacial ice flows, stress fractures that run tens of metres deep form in the glacier's surface (pictured). These crevasses increase the rate of ice movement, which creates more cracks in a self-reinforcing loop that has the potential to exacerbate ice loss from the land and contribute to rising sea levels. Writing in *Nature Geoscience*, Chudley *et al.* report that in most parts of Greenland, ice crevasses in glaciers are getting deeper and larger — and this is happening more quickly than previously estimated (T. R. Chudley *et al. Nature Geosci.* https://doi.org/n5bg; 2025).

Using satellite images gathered in 2016 and 2021, the authors created 3D maps of crevasses across the Greenland Ice Sheet, the second biggest ice mass on Earth. Chudley *et al.* found that increases in crevasse volume were most extreme where fast-moving glaciers meet the sea, and that the acceleration of crevassing coincided with quickened ice flow caused by a rise in air and ocean temperatures. Predictions of future ice-sheet dynamics will be aided by the vast data set, and the researchers already warn that the effects of crevassing could worsen over the next few years as one of Greenland's fastest-flowing glaciers picks up speed.

Holly Smith

are yet to be discovered. Expanding genomic studies to include under-represented bat families could provide molecular insights into their resilience against diverse viruses.

Furthermore, Morales *et al.* found that the ISG15 protein from bat species that harbour SARS-CoV-2-related coronaviruses is more effective at blocking SARS-CoV-2 than is ISG15 from other bat species. A study published last year showed that certain SARS-CoV-2 proteins, such as the nucleocapsid (N) protein, can be ISGylated[7]. ISGylation of the N protein impairs the synthesis of viral RNA molecules, and thereby inhibits SARS-CoV-2 replication[7]. Investigating whether specific bat species exhibit enhanced ISGylation of coronaviral N proteins could clarify why bats tolerate coronavirus infections that are highly pathogenic in humans. Moreover, the activation of key host proteins in antiviral immunity requires ISG15 conjugation[8,9]. Further studies are needed to establish the precise mechanisms through which adaptations in the bat ISG15 protein confer viral resistance.

The implications of this work extend beyond bats. Integrating genomic data with cutting-edge approaches — such as single-cell transcriptomics to catalogue the RNA transcripts expressed in individual cells, and comparative proteomics analyses to assess the differences in protein expression between bats and humans — could unveil molecular targets for alleviating excessive inflammation in humans. As well as *ISG15*, several other immune genes that underwent positive selection in bats were identified, and these will require functional validation. Decoding bats' viral disease resistance will be crucial for mitigating future pandemics caused by 'spillover' events in which viruses are transmitted from animals to humans. It will also provide valuable insights to aid the design of therapeutic strategies for human disorders that are driven by overactive inflammation.

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The authors declare no competing interests.
This article was published online on 29 January 2025.