ECOLOGY

Resilient meerkats

Meerkats (*Suricata suricatta*) living in the Kalahari Desert must cope with extreme variations in temperature and rainfall throughout the year. Writing in *Science*, Maria Paniw and colleagues report that these variations alter the animals' body mass, and that body-mass changes have different effects on meerkat populations depending on when they happen (M. Paniw *et al. Science* **363**, 631–635; 2019).

For example, low rainfall just before the breeding season starts leads to food scarcity, low body mass, low reproductive success and an increased risk of population extinction. But a warm environment during the non-breeding season can increase body mass and lead to more efficient reproduction, compensating for previous losses in population size.

The findings are of broad interest because species living in extreme seasonal environments, such as meerkats, give us a glimpse of the ecological effects of future changes in Earth's climate. **Joana Osório**

KLEIN & HUBERT/NPL

VIROLOGY

Hosts combat Ebola using protein disguise

Infection by Ebola virus can be fatal. The discovery of a human protein that mimics one type of Ebola protein and binds to another to suppress viral RNA production might aid the development of clinical treatments for the disease.

SEIYA YAMAYOSHI & YOSHIHIRO KAWAOKA

The natural hosts for the Ebola virus are thought to be bats. However, this RNA virus can also infect humans, and there have been numerous reported outbreaks of the viral infection originating in African countries over the past 40 years[1]. The largest such outbreak was between 2013 and 2016, and resulted in 28,616 suspected cases and 11,310 deaths, mainly in Guinea, Liberia and Sierra Leone (go.nature.com/2qtbj6i). The fatality rate can be high: for example, an outbreak that began in 2018 in the Democratic Republic of the Congo has so far resulted in 685 cases of infection and 419 deaths, a fatality rate of approximately 60% (go.nature.com/2qtdirv).

Ebola infection begins with fever, muscle pain and headache, followed by vomiting, diarrhoea, rash and symptoms of impaired kidney and liver function. Basic supportive care for those infected, such as treatment to combat dehydration, can help to prevent it being fatal[2]. However, in addition to managing symptoms, there is a need to develop other approaches that prevent or treat the disease, such as vaccines, antiviral therapies or antibody treatments[3–6]. Although there have been some clinical trials, no drugs or vaccines have yet been approved for clinical use. And because it can't be predicted where the next Ebola outbreak will occur, it is difficult to identify those most at risk of infection, and so plan a vaccination strategy. Writing in *Cell*, Batra *et al.*[7] report their investigation of natural host defences against the Ebola virus. Their identification of a human protein that can affect the success of viral replication might open new avenues of research into antiviral treatments.

Batra and colleagues expressed tagged versions of Ebola proteins individually in human cells grown *in vitro*, and used co-immunoprecipitation and mass spectrometry techniques to identify human proteins that interacted with viral proteins. They used this information to generate a map of the network of such interactions — termed an interactome map. The authors found 194 interactions between host and viral proteins, one of which was between the human protein RBBP6 — a type of enzyme called a ubiquitin ligase — and an Ebola protein called VP30. Various Ebola proteins, including VP30, function in the viral polymerase protein complex, which makes

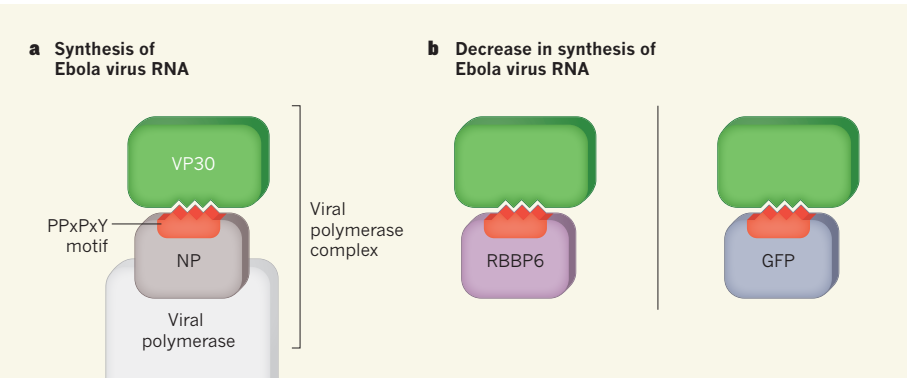

Figure 1 | Protein interactions and a host defence response to Ebola virus infection. a, When the Ebola virus infects human cells, the virally encoded proteins VP30 and NP interact[8], helping to boost the synthesis of Ebola virus RNA. NP binds to the viral polymerase enzyme, and is part of the viral polymerase protein complex that makes viral RNA. Batra *et al.*[7] report that a motif of amino-acid sequences termed PPxPxY has a key role in the interaction between VP30 and NP. **b**, To uncover possible host defences against infection by Ebola virus, the authors used human cells grown *in vitro* to test for host proteins that could bind to proteins encoded by the virus. They report that the human protein RBBP6 has a PPxPxY motif through which it binds to VP30. Because this binding inhibits the interaction of NP with VP30, it helps to limit the synthesis of Ebola virus RNA in human cells grown *in vitro*. The authors report that if a peptide that contains the PPxPxY motif is fused to green fluorescent protein (GFP), the resulting chimaeric protein also inhibits this viral RNA synthesis in human cells grown *in vitro*.

viral RNA, and Batra and colleagues transferred DNA sequences encoding these proteins into human cells grown *in vitro*. They found that the expression of VP30, at both the RNA and protein level, depended on the level of RBBP6, with high levels of RBBP6 being associated with low levels of VP30 expression and with low activity of the viral polymerase complex. When the authors used a technique called gene silencing to reduce the expression of RBBP6 in the human cells expressing Ebola proteins, the activity of the Ebola viral polymerase complex and viral replication was increased.

The authors carried out an X-ray structural analysis to model the interaction between VP30 and RBBP6. These structural results, and those from their other experiments investigating protein binding to VP30, revealed that a key feature of interest in RBBP6 is a sequence of 23 amino-acid residues (a peptide) that includes a motif called PPxPxY (in which P is the amino acid proline, Y is the amino acid tyrosine and x is any other amino-acid residue). This motif inserts into a cleft in VP30 that is known[8] to bind to an Ebola protein called NP (Fig. 1). NP is part of the viral polymerase complex and serves as a scaffold that binds to viral RNA. VP30 binding to NP promotes viral RNA synthesis. The researchers noted that the PPxPxY motif is also present in NP in a region that binds to VP30. This suggests that NP and RBBP6 might compete for binding to VP30.

In *in vitro* experiments, Batra *et al.* showed that the binding between RBBP6 and VP30 was five times stronger than that between NP and VP30, indicating that RBBP6 should have the capacity to effectively sequester VP30 from NP. Their experiments suggest that this peptide motif alone has a key role in limiting the interaction between VP30 and NP. Furthermore, if, instead of RBBP6, an engineered chimaeric protein composed of a PPxPxY-containing peptide and a fluorescent marker called green fluorescent protein was expressed in human cells expressing Ebola proteins, the chimaeric protein decreased Ebola polymerase complex activity and viral propagation compared with the effect observed in cells that received only green fluorescent protein.

Because Batra and colleagues' approach to identifying the interactions between viral and host proteins is based on the expression of single types of viral protein, it does not identify host-protein interactions that might occur only when viral proteins are part of multi-protein complexes. Further analyses will therefore be needed to identify any such interactions, and to verify that the interactome map is correct. Also, because these experiments were conducted using genetic-engineering techniques, rather than studying a natural process of viral infection of human cells, it is difficult to assess the extent to which these events ultimately affect the level of viral replication. It is possible that, like other host antiviral proteins, RBBP6 levels vary and are subject to regulation by unknown mechanisms. Further study is needed to understand exactly how RBBP6 affects Ebola virus replication.

During the 2013–16 Ebola outbreak[9,10], no mutations in VP30 were reported in the region of the protein that corresponds to the RBBP6 binding site. This suggests that evolutionary selective pressure to evade host targeting by RBBP6 is limited, or that a viral mutation that drives resistance to RBBP6 is not selected for because it has a detrimental effect on the virus — possibly because such a mutation might also affect an interaction between VP30 and NP that is essential for viral replication. It would be interesting to test whether bats inhibit Ebola virus replication using RBBP6.

A key discovery of this study is that a peptide that includes the PPxPxY motif, when fused to green fluorescent protein, is sufficient to inhibit virus replication *in vitro* (the effect *in vivo* was not evaluated). The cleft on VP30 to which this peptide binds could therefore be a promising target for efforts to develop antivirals against Ebola. Although it is not known whether the peptide inhibits viral replication when it is not fused to green fluorescent protein, this discovery could provide a starting point for developing and optimizing other small compounds that inhibit viral replication. That might lead to the development of a class of antiviral that has high specificity for the Ebola virus. ■

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1. Boisen, M. L. *et al. Annu. Rev. Virol.* **3**, 147–171 (2016).
2. Duraffour, S., Malvy, D. & Sissoko, D. *Curr. Opin. Virol.* **24**, 9–15 (2017).
3. Henao-Restrepo, A. M. *et al. Lancet* **389**, 505–518 (2017).
4. Saphire, E. O. *et al. Cell* **174**, 938–952 (2018).
5. Marzi, A. *et al. Science* **348**, 439–442 (2015).
6. Sakurai, Y. *et al. Science* **347**, 995–998 (2015).
7. Batra, J. *et al. Cell* **175**, 1917–1930 (2018).
8. Kirchdoerfer, R. N., Moyer, C. L., Abelson, D. M. & Saphire, E. O. *PLoS Pathog.* **12**, e1005937 (2016).
9. Urbanowicz, R. A. *et al. Cell* **167**, 1079–1087 (2016).
10. Diehl, W. E. *et al. Cell* **167**, 1088–1098 (2016).

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OCEAN BIOGEOCHEMISTRY

A diagnosis for marine nitrogen fixation

Nitrogen gas dissolved in the ocean must be fixed — converted into more-reactive compounds — before it can be used to support life, but the regions in which this nitrogen fixation occurs have been elusive. Not any more. SEE ARTICLE P.205

NICOLAS GRUBER

In 1934, the oceanographer Alfred C. Redfield took a leap into the unknown. He posited[1] that marine nitrogen-fixing organisms — microorganisms that convert nitrogen gas (N_2) dissolved in the sea into 'fixed' nitrogen compounds that can be used by other organisms to sustain life — might help to explain why the ratio of fixed nitrogen (N) and phosphorus (P) in sea water is similar to their ratio in marine phytoplankton, even though no nitrogen-fixing organisms had been identified at the time. Since then, the search for the regions in which nitrogen fixation occurs, and the role of fixation in controlling the marine nitrogen cycle, have engaged biogeochemists and biologists alike[2]. But despite much progress, the patterns, rates and limiting factors that control marine nitrogen fixation have remained elusive[3].

In 2007, a study[4] that used a geochemical method called the P* approach suggested that a large fraction of marine nitrogen fixation occurs in the eastern tropical Pacific Ocean. This is a region in which depleted oxygen levels in the water column cause fixed nitrogen to be converted back to N_2, a process called denitrification. The P* approach analyses the relative abundance of nitrate (the major form of fixed nitrogen) and phosphate in sea water, and estimates the transport and mixing of these nutrients using an ocean-circulation model. In contrast to the results of the P* method, direct measurements of nitrogen-fixation rates suggest that there is a clear spatial separation between nitrogen fixation and denitrification[5–7]. On page 205, Wang *et al.*[8] suggest a way of reconciling the results of these two approaches.

The authors pick up many of the threads initially laid out by Redfield and also used in the P* approach. Thus, they use a diagnostic model to work out the sources and sinks of fixed nitrogen and phosphorus implied by the transport and mixing of nitrate and phosphate in sea water, and compare this with the N:P ratio in marine phytoplankton