charge. The authors suggest that up to a third of the southern temperature signal is due to this current, and that the remaining two-thirds is associated with the thermal-seesaw effect and changes in the large-scale MOC.

The classical bipolar seesaw and Knutti and colleagues' revised thermal–freshwater seesaw are intriguing, as they present physically based models to explain a set of observations. And indeed, the modelled temperature results fit very well with the ice-core temperature changes (Fig. 5 on page 855). To test all aspects of the new concept, however, more evidence is necessary, for example data on the strength of the overturning circulation. An obvious test for future studies would be to see how much of the variability observed in Antarctic temperature data can be explained by freshwater data from the North Atlantic.

The various versions of the bipolar seesaw model assume that climate changes in the Northern Hemisphere trigger a response in the Southern Hemisphere. And some evidence for a northern trigger is provided by the fact that observed increases in fresh water discharged into the North Atlantic follow the pattern predicted by the models relative to the ice-core temperature data (Fig. 1). However, an increasing number of calculations suggest that Antarctic temperature changes precede those in Greenland by 1,000–2,000 years[2,9]. Therefore, an alternative theory is that the trigger lies in the Southern Hemisphere. Model experiments[10–12] and ocean sediment-core data[13,14] suggest that a variety of processes in the Southern Hemisphere might have provoked changes in the MOC. These include changes in the strength of westerly winds and the circumpolar current; changes in Southern Ocean density structure; and gradual warming triggered by a shift in the main source of water entering the South Atlantic, either via the warm Indian Ocean or the cold Pacific Ocean.

For now, the notion of a southern trigger for climate changes is an interesting theory that lacks a conceptual model able to explain all the observations from Antarctica and Greenland. Regardless of whether north or south leads in DO events, we need to understand better why shifts in the MOC occur. However, conflicting evidence and numerous diverse lines of argument on how the climate of the two hemispheres is linked confuse the issue. At present, we lack the necessary data from the northern and southern oceans to put palaeoceanographic constraints on the past history of MOC mode switches from this bipolar perspective. In any event, understanding the cause and effect of previous abrupt climate changes is crucial for a rational assessment of the probability of such events occurring in the future. ■

Trond M. Dokken and Kerim H. Nisancioglu are at the Bjerknes Centre for Climate Research, University of Bergen, Allégaten 55, Bergen 5007, Norway.
e-mail: trond.dokken@bjerknes.uib.no

1. Knutti, R., Flückiger, J., Stocker, T. F. & Timmermann, A. *Nature* **430,** 851–856 (2004).
2. Blunier, T. *et al. Nature* **394,** 739–743 (1998).
3. Broecker, W. S. *Paleoceanography* **13,** 119–121 (1998).
4. Crowley, T. J. *Paleoceanography* **7,** 489–497 (1992).
5. Stocker, T. F. *Science* **282,** 61–62 (1998).
6. Steig, E. J. & Alley, R. B. *Ann. Glaciol.* **35,** 451–456 (2002).
7. Schmittner, A. *et al. Quat. Sci. Rev.* **22,** 659–671 (2003).
8. Stocker, T. F. & Johnsen, S. J. *Paleoceanography* **18,** doi:0.1029/2003PA000920 (2003).
9. Hinnov, L. A. *et al. Quat. Sci. Rev.* **21,** 1213–1228 (2002).
10. Toggweiler, J. R. & Samuels, B. *Deep-Sea Res. I* **42,** 477–500 (1995).
11. Knorr, G. & Lohmann, G. *Nature* **424,** 532–536 (2003).
12. Weaver, A. J. *et al. Science* **299,** 1709–1713 (2003).
13. Ninnemann, U. S. & Charles, C. D. *Earth Planet. Sci. Lett.* **201,** 383–396 (2002).
14. Peeters, F. J. C. *et al. Nature* **430,** 661–665 (2004).
15. Dokken, T. M. & Jansen, E. *Nature* **401,** 458–461 (1999).

Structural biology

Anthrax hijacks host receptor

James G. Bann and Scott J. Hultgren

An atomic picture of how anthrax toxin binds to its host's cells reveals that the toxin commandeers a host receptor protein and tricks it into helping the toxin enter the cell.

In 2001, *Bacillus anthracis* made headlines when US Senators Thomas Daschle and Patrick Leahy received letters containing anthrax spores, highlighting the urgent need for an effective treatment against the bacterium. Once exposed to *B. anthracis*, the only treatment available involves a 60-day course of antibiotics that have unpleasant side-effects[1]. The race to develop more palatable alternatives that will work at any stage of infection is now focusing on anthrax toxin, the protein complex responsible for the bacterium's lethal effects.

On page 905 of this issue, Liddington and colleagues[2] report the X-ray crystal structure of one of the anthrax toxin proteins, the protective antigen (PA), bound to its receptor from the host's cell, capillary morphogenesis protein 2 (CMG2). This work explains the structural basis of how anthrax toxin recognizes CMG2, and suggests a mechanism by which CMG2 is duped into behaving as a molecular switch that controls the transfer of anthrax toxin into the cell's cytosol, an event that ultimately proves fatal to the host.

Anthrax toxin is composed of three proteins: protective antigen (so named because it is used as a vaccine), oedema factor and lethal factor. PA is a large protein consisting of four domains (I–IV), primarily involved in targeting the toxin to host cells by recognizing CMG2. The crystal structure[2] reveals that the high-affinity binding of PA with CMG2 (ref. 3) is due partly to the involvement of a magnesium ion at the interface between them. A key aspartic acid residue

Oceanography

Islands in the stream

During the *Beagle*'s visit to the Galapagos Islands in 1835, Charles Darwin noted that the local climate was far less warm than would be expected from the islands' position on the Equator. The air-conditioning effect is due to the cooling influence of the surrounding oceans — part of which, according to C. Eden and A. Timmermann (*Geophys. Res. Lett.* **31,** L15308; 2004), arises from the very presence of the islands.

As this satellite image shows, the Galapagos are isolated in the vastness of the Pacific Ocean, lying about 1,000 km west of South America. This is nonetheless an oceanographically sensitive location, because the islands obstruct two components of a system of wind-driven ocean currents in the equatorial Pacific. The cool Southern Equatorial Current flows westwards as part of the Pacific subtropical gyre, and splits into a northern and a southern branch at the Galapagos. The subsurface Equatorial Undercurrent transports water eastwards between and beneath these two branches, and almost stops dead where it hits the islands.

Using a high-resolution numerical model, Eden and Timmermann have simulated equatorial Pacific currents with and without the Galapagos topography. The differences are significant. The islands produce

a wake-like pattern in both currents, with flow anomalies extending up to 2,000 km in an east–west direction. And as a result of stronger upwelling of cooler water from depth, sea surface temperatures just west of the Galapagos are up to 2 °C lower than they would otherwise be — hence the comparatively temperate climate. **Heike Langenberg**

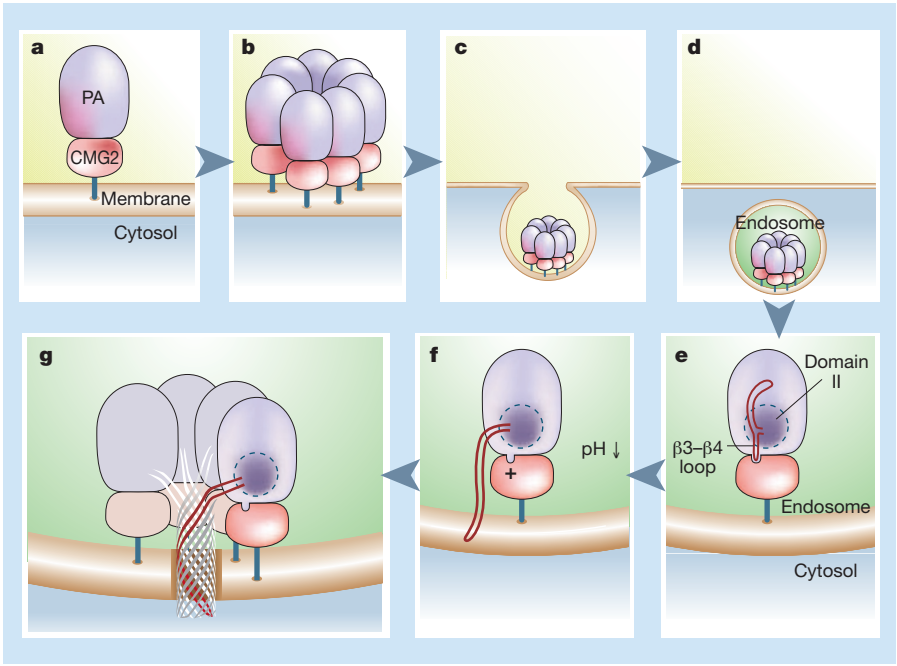

Figure 1 **Throwing the anthrax switch. Liddington and colleagues[2] suggest how anthrax toxin tricks a host cell receptor into helping it into the cell. a, The anthrax protective antigen (PA) binds the host capillary morphogenesis protein 2 (CMG2) on the outside of the cell. b, Seven PA–CMG2 modules link together to form a heptameric complex, which binds to the other anthrax toxin proteins, oedema factor and lethal factor (not shown). c, A deep pocket forms in the cell membrane. d, The neck of the pocket is pinched off, leaving the toxin–receptor complex inside the endosome. e, f, The molecular switch. For simplicity, a single PA–CMG2 monomer is shown. When PA binds to CMG2 (e), a loop of PA domain II (β3–β4) is gripped in a groove on the CMG2 surface. Inside the endosome (f) the pH decreases, generating a positive charge in the CMG2 groove. This repels the β3–β4 loop, resulting in a large conformational change in PA domain II. The loop and some neighbouring strands peel away and insert into the endosome membrane. g, They twist around strands from neighbouring PA–CMG2 modules to form a pore, allowing the oedema factor and the lethal factor into the host cytosol.**

in domain IV of PA works in conjunction with a metal-ion-dependent adhesion site (MIDAS) on CMG2 to coordinate the ion.

An atomic structure of CMG2 (ref. 4) revealed that it is very similar to a domain in proteins called integrins, which mediate the attachments between cells and the extracellular matrix. So a fascinating feature of the new crystal structure[2] is the discovery that PA does indeed recognize CMG2 using a similar mechanism to the one by which extracellular matrix proteins bind to integrins. Specifically, PA binds to CMG2 in a manner similar to the way in which extracellular matrix protein type IV collagen recognizes α2β1 integrin[5]: the collagen uses an aspartic acid to help coordinate a magnesium ion together with a MIDAS site on the integrin. But this raises a question: if integrins and CMG2 are so similar structurally, how does the anthrax toxin tell them apart? Unexpectedly, the crystal structure[2] shows that domain II of PA has a small β-hairpin loop (β3–β4) that fits snugly into a groove on the CMG2 surface. Integrins do not have a comparable groove, explaining how PA is able to discriminate between them and CMG2.

Once PA binds to CMG2 on the host-cell surface, a protease clips PA in two. The smaller portion diffuses away, and the larger part remains bound to the CMG2 receptor, eventually forming a complex of seven PA–CMG2 modules, called a pre-pore[6]. The oedema factor and/or the lethal factor bind to this PA–CMG2 complex, triggering a process called endocytosis, by which the PA–CMG2 complex is engulfed into the cell (Fig. 1). The area of the cell membrane containing the toxin–receptor complex forms a deep pocket into the cell. The neck of the pocket is pinched off to create a bubble-like organelle, an endosome, with the toxin–receptor complex inside, still attached to the membrane. To inject the oedema factor and the lethal factor into cells, the seven PA molecules must act together to form a straw-like structure — a pore — bridging the endosome membrane and opening out into the cell cytosol (Fig. 5 on page 907). The pore transfers the oedema factor and the lethal factor to the cytosol, leading ultimately to cell death through the disruption of vital physiological processes[7,8].

Liddington and colleagues' crystal structure[2] reveals a molecular-switching mechanism in the complex that might control the formation of this pore (Fig. 1). The groove on CMG2 that interacts with PA domain II contains a crucial residue (histidine 121) that holds the PA in the right conformation until it is ready to insert into the endosome membrane. But what throws this molecular switch so that the toxin can enter the cell? The authors propose that the answer might be in the pH of the local environment. Their model (Fig. 1e–g) suggests that once the endosome is formed, the internal pH decreases and histidine 121 is protonated, becoming positively charged. This repels a nearby arginine on PA, reducing the affinity of the β3–β4 loop of PA for CMG2. Consequently, the PA domain II undergoes a large conformational change, with the β2–β3 strands adjacent to the β3–β4 loop peeling away from PA like the skin of a banana peeling away from the fruit. The β2–β3 strands are lined with several histidines, and protonation of these probably helps this unwrapping process[9]. Once free of CMG2 and PA, the strands insert into the endosome membrane and form the pore by twisting around the strands from the six neighbouring PA molecules[9]. Essentially, CMG2 acts as a pH-sensitive switch, holding the PA in the right shape until just the right time, before releasing it to form the pore.

CMG2 was discovered only recently, and it is proposed to have a role in the assembly of the basement membrane, the meshwork of extracellular matrix proteins that helps to support cells[10]. Although the normal biological function of CMG2 is as yet unclear, presumably it is not to facilitate translocation of anthrax toxin into the cell. Rather, Liddington and colleagues' analysis[2] suggests that anthrax toxin hijacks CMG2, employing it as a molecular switch to help release the toxin into the cell. This structure will provide a good starting point for evaluating the energetics and mechanism of pore formation, enabling the design of drugs aimed at derailing the critical early steps of anthrax function. It could also provide clues to how other pore-forming toxins, such as α-haemolysin from *Staphylococcus aureus*, undergo such large conformational changes[11]. ■

James G. Bann is in the Department of Chemistry, Wichita State University, Wichita, Kansas 67260-0051, USA.
Scott J. Hultgren is in the Department of Molecular Microbiology, Washington University School of Medicine, St Louis, Missouri 63110, USA.
e-mails: jim.bann@wichita.edu hultgren@borcim.wustl.edu

1. Jefferds, M. D. *et al. Emerg. Infect. Dis.* **8,** 1138–1144 (2002).
2. Santelli, E., Bankston, L. A., Leppla, S. H. & Liddington, R. C. *Nature* **430,** 905–908 (2004).
3. Wigelsworth, D. J. *et al. J. Biol. Chem.* **279,** 23349–23356 (2004).
4. Lacy, D. B. *et al. Proc. Natl Acad. Sci. USA* **101,** 6367–6372 (2004).
5. Emsley, J., Knight, C. G., Farndale, R. W., Barnes, M. J. & Liddington, R. C. *Cell* **101,** 47–56 (2000).
6. Petosa, C., Collier, R. J., Klimpel, K. R., Leppla, S. H. & Liddington, R. C. *Nature* **385,** 833–838 (1997).
7. Leppla, S. H. *Proc. Natl Acad. Sci. USA* **79,** 3162–3166 (1982).
8. Park, J. M., Greten, F. R., Li, Z. W. & Karin, M. *Science* **297,** 2048–2051 (2002).
9. Blaustein, R. O., Koehler, T. M., Collier, R. J. & Finkelstein, A. *Proc. Natl Acad. Sci. USA* **86,** 2209–2213 (1989).
10. Bell, S. E. *et al. J. Cell Sci.* **114,** 2755–2773 (2001).
11. Galdiero, S. & Gouaux, E. *Protein Sci.* **13,** 1503–1511 (2004).