in models of iron chemistry in the surface ocean. The problem is that such models often fail to reproduce the observed distributions of dissolved iron in seawater[6].

In fact, dissolved iron is a complex mixture of species that are aqueous and solid, organic and inorganic[8]. Dissolved iron is therefore now often subcategorized into soluble and colloidal fractions. Soluble iron is close to what is generally considered to be truly dissolved iron and is mainly thought to be dominated by iron-bound ligands, whereas colloidal iron consists of solids about 2–200 nanometres in diameter. This subcategorization has been a big step forward for research in marine systems, creating many opportunities for investigations of the poorly described colloidal-iron pool.

In this context, Tagliabue *et al*. now report new, accurate measurements of the concentrations of dissolved iron, ligands and particulate iron in a region of the Sargasso Sea in the Atlantic Ocean. Notably, the data provide the first record of seasonal patterns of variation for ligands and dissolved iron. This allowed the authors to represent the seasonal ligand variation accurately in a cutting-edge numerical model of the global ocean iron cycle (the PISCES–Quota model), to test whether this model could correctly simulate the observed variations of dissolved iron. The authors found that the depth and seasonal distributions of dissolved iron were poorly simulated, especially in the upper ocean, indicating that iron–ligand binding alone is insufficient to explain the observed levels of dissolved iron.

The team therefore developed a conceptual model of iron cycling that includes a pool of colloidal iron that is out of equilibrium with ligands (Fig. 1) — a change that means the concentration of dissolved iron is no longer controlled simply by ligand concentration. The new model allows colloidal iron to aggregate into particles that sink to the deep ocean, a mechanism that the authors call the colloidal shunt. When the colloidal shunt was incorporated into PISCES–Quota, the refined numerical model reproduced the authors' observational data better than did the original model, including the data for particulate iron.

Tagliabue *et al*. then applied this refined model to the global ocean, and again found that it reproduced observational data better than did the original PISCES–Quota model. Moreover, the simulations suggested that most ocean regions can be categorized into one of three groups, according to the dominant mode of iron cycling in seawater: areas characterized by high biological activity, which are dominated by biological cycling of iron; regions with low biological activity, dominated by the effects of iron–ligand binding; and areas that receive direct inputs of iron (such as windblown Saharan dust), which are dominated by the colloidal shunt. Moreover, the simulations indicate that iron cycling in the upper water column through the colloidal shunt is important in about 40% of the ocean.

A limitation of the study is that the authors did not report the concentrations of colloidal iron in their fieldwork. This is ironic, because their findings provide a strong argument for colloidal iron to be analysed routinely along with dissolved and particulate fractions. The work also points to large gaps in our knowledge of the physical and chemical properties of colloidal iron: the mineralogy and aggregation–disaggregation mechanism (or mechanisms) are unknown. Direct observations of the properties of colloidal iron from field and laboratory studies are needed. Moreover, the fate of colloidal iron once it grows into larger particles is unclear — is it deposited in sediments, or does it undergo some form of recycling deeper in the water column?

Nevertheless, by reconciling the previously persistent mismatch between observations and models, and by determining the main iron-cycling processes that occur in different ocean settings, Tagliabue and colleagues' work is a major advance for ocean biogeochemistry. The findings will aid our understanding of how modern climate change will progress, and of past feedbacks between the ocean, atmosphere and biosphere.

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1. Moore, C. M. *et al*. *Nature Geosci*. **6**, 701–710 (2013).
2. Tagliabue, A. *et al*. *Nature* **620**, 104–109 (2023).
3. Schwertmann, U. *Plant Soil* **130**, 1–25 (1991).
4. Kraemer, S. M. *et al*. *Rev. Mineral. Geochem*. **59**, 53–84 (2005).
5. Fitzsimmons, J. N. & Boyle, E. A. *Geochim. Cosmochim. Acta* **125**, 539–550 (2014).
6. Tagliabue, A. *et al*. *Glob. Biogeochem. Cycles* **30**, 149–174 (2016).
7. Gledhill, M. & Buck, K. N. *Front. Microbiol*. **3**, 69 (2012).
8. Fitzsimmons, J. N. & Conway, T. M. *Annu. Rev. Mar. Sci* **15**, 383–406 (2023).

The author declares no competing interests.

Cell biology

Hotly awaited structures of the human protein UCP1

Michael J. Gaudry & Martin Jastroch

The protein UCP1 helps to release energy as heat in brown fat. Structures of human UCP1 provide crucial information about its mechanism of action, and might aid drug design for obesity and various metabolism-associated complications. **See p.226**

Organelles called mitochondria act as the powerhouses of our cells. Furthermore, through the action of the protein UCP1, mitochondria can be 'supercharged' to provide extra heat. On page 226, Kang and Chen[1] shed light on the structure of human UCP1.

Mitochondria harvest the energy from food by means of cellular respiration, building up a gradient of hydrogen ions (protons) across the mitochondrial inner membrane. This gradient is harnessed to make the molecule ATP, the common energy currency of cells. In mammals, mitochondria are particularly abundant in a tissue called brown fat, in which their main role is to maintain a high body temperature in cold environments. Instead of helping to make ATP, these mitochondria uncouple respiration from ATP production through the 'proton leak' activity of the protein UCP1 (Fig. 1), which dissipates the proton gradient, and heat-releasing oxidation reactions are accelerated in an attempt to maintain the gradient[2].

Obesity and other metabolism-associated complications, such as type 2 diabetes, are caused by the consumption of more calories than are burnt, increasing lipid deposition in white fat and other organs. The fact that excess calories can be burnt by increasing the mitochondrial energy turnover has sparked broad biomedical interest in exploiting this feature as a promising avenue for therapy.

Obese adult humans have limited amounts of brown fat, and so major efforts have been invested in trying to induce UCP1 expression in white fat[3]. To maximize energy consumption, however, UCP1 must be activated. It has long been known that natural UCP1 activators and inhibitors exist in the body — these are, respectively, molecules such as fatty acids and purine nucleotides (for example, ATP)[2]. But there is little consensus about how these modulators interact with UCP1, or how protons are transported[4] through it. A major bottleneck for study of the protein has been the absence of a structure for UCP1. This clouds interpretation of structure–function relationships, and hampers the design of

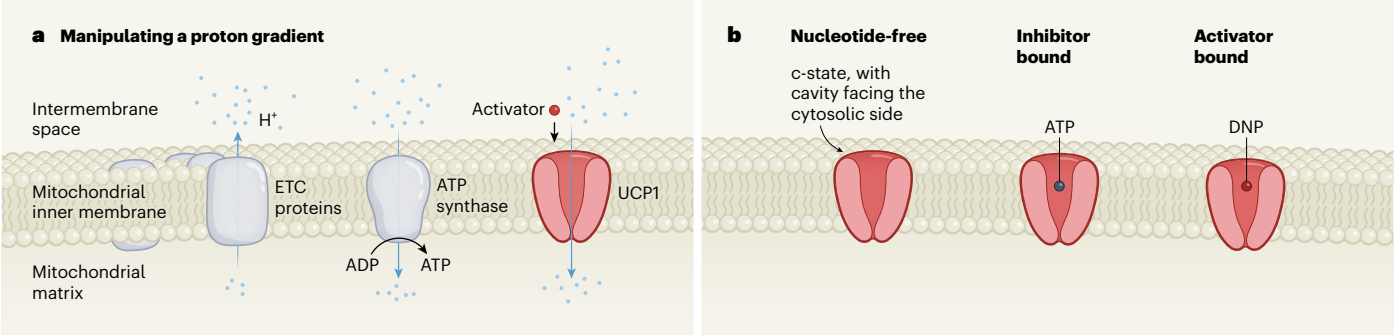

Figure 1 | The human protein UCP1. a, In organelles called mitochondria, a gradient of hydrogen ions (protons, H^+) is built up across the mitochondrial inner membrane by means of proteins of the electron-transport chain (ETC). Protons in the organelle's interior (the mitochondrial matrix) move to the intermembrane space, in the direction towards the cytosol. The enzyme ATP synthase harnesses the proton gradient and the molecule ADP to produce ATP, the molecule that provides energy for cells. However, the mitochondria of cells in brown fat express the protein UCP1 in their inner membrane, and this protein can dissipate the proton gradient when activated. UCP1 activation helps to burn calories and produce heat through events that occur in the effort to restore the gradient. **b**, Kang and Chen[1] present structural data for UCP1 using single-particle cryo-electron microscopy. The authors report the protein's structure in three conditions: nucleotide-free; bound to ATP, which inhibits UCP1; and bound to an artificial activator of UCP1 called DNP. All three structures display a configuration described as a c-state conformation, in which an accessible central cavity faces the cytosolic side of the mitochondrial inner membrane.

UCP1-targeted drugs.

Kang and Chen deliver a breakthrough in the understanding of UCP1 function by determining high-resolution structures of human UCP1 at approximately 2.5 ångströms. Given the instability of this membrane protein and its small size (33 kilodaltons), retrieving structural information using single-particle cryo-electron microscopy, the state-of-the-art technology for structural analysis, is not straightforward[5].

To overcome the technical hurdles, the authors chose an innovative route. They developed a scaffold for UCP1 using synthetic structures called nanobodies (also dubbed sybodies) to stabilize the protein[6], combined with a strategy (using a component called a legobody) for increasing the size of a UCP1 complex[5]. Crucially, when this enlarged complex is reconstituted in lipid vesicles called liposomes, UCP1 retains its ATP-sensitive proton-leak function, enabling the authors to draw function-related conclusions from the structures obtained.

The structure of UCP1, determined in conformations when bound and not bound to its natural inhibitor ATP, sheds light on the protein superfamily SLC25 to which UCP1 belongs. SLC25 consists of more than 50 mitochondrial proteins that function as molecular carriers. Previously, the structure of only the SLC25 carrier protein AAC1 had been obtained, in that case by locking stable protein complexes using potent plant toxins[7].

UCP1 consists of six membrane-spanning segments of α-helices, each linked by loops and, on the inner (matrix) side of the mitochondrial inner membrane, by short helices, similar to those found in AAC1. Experiments into the effects of mutating various amino acids in the protein, combined with an assessment of protein stability, revealed that a positively charged central cavity is formed that attracts and selectively binds negatively charged purine nucleotides (such as ATP and ADP) to key residues. UCP1's central cavity is 'gated' by networks of salt bridges (close-range electrostatic interactions) on the edges of the cavity facing the cytosolic or the matrix side.

Kang and Chen determined the human UCP1 structure in three pivotal conditions: nucleotide-free; bound to its inhibitor ATP; and bound to the artificial activator molecule 2,4-dinitrophenol (DNP)[8]. Under nucleotide-free and ATP-bound conditions, UCP1's central cavity is open in the direction of the cytosol, a conformation termed the c-state. In this conformation, the matrix ring-like gate is tightly closed, revealing no obvious route for protons to enter the interior of the mitochondrion. These structural data are consistent[9] with the conformation of UCP1 when bound to the molecule GTP and with expectations that, in its natural cellular environment, UCP1 remains inhibited before its activation[10].

With the inhibitor-bound UCP1 in the c-state, one would expect the active, proton-conducting UCP1 to be in the m-state, in which the central cavity is open to the interior of the organelle (the mitochondrial matrix). Transitioning between c- and m- states would be similar to the established carrier-like mechanism of AAC1, in which the protein uses both conformations to exchange ADP and ATP across the mitochondrial inner membrane[7]. Notably, UCP1 has all the structural features required for a carrier-like transport mechanism[9]. However, Kang and Chen find that DNP competes with ATP for the same binding site, and that DNP stabilizes active UCP1 in the c-state (Fig. 1). The authors suggest that UCP1 might increase proton leak while remaining in the c-state, with DNP providing stepping-stone-like sites enabling protons to 'jump' from one 'protonatable' site to the next through the central cavity and across the matrix gate.

An immobile c-state conformation could be a unique property of UCP1, and might not require a carrier-like state transition to transport protons. However, previous protein-stability studies suggest that UCP1 undergoes major conformational changes on activation by fatty acids[11]. Do fatty acids compete for the same binding site as the one for purine nucleotides, similar to DNP, and might naturally occurring fatty acids induce m-state conformational changes? Further structural information will be needed to unravel how such natural activators bind to UCP1, and to pinpoint the precise mechanism of proton transport.

In today's era of research into human brown fat, Kang and Chen's work represents a momentous achievement. By presenting the structure of UCP1 in multiple arrangements and highlighting key structural features, this study opens the door to future work on targeted drug design that might help to alleviate the burden of metabolic diseases.

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1. Kang, Y. & Chen, L. *Nature* **620**, 226–231 (2023).
2. Jastroch, M., Divakaruni, A. S., Mookerjee, S., Treberg, J. R. & Brand, M. D. *Essays Biochem.* **47**, 53–67 (2010).
3. Singh, A. M. *et al. Nature Commun.* **11**, 2758 (2020).
4. Crichton, P. G., Lee, Y. & Kunji, E. R. S. *Biochimie* **134**, 35–50 (2017).
5. Wu, X. & Rapoport, T. A. *Proc. Natl Acad. Sci. USA* **118**, e2115001118 (2021).
6. Zimmermann, I. *et al. eLife* **7**, e34317 (2020).
7. Ruprecht, J. J. *et al. Cell* **176**, 435–447 (2019).
8. Bertholet, A. M. *et al. Nature* **606**, 180–187 (2022).
9. Jones, S. A. *et al. Sci. Adv.* **9**, eadh4251 (2023).
10. Jastroch, M., Hirschberg, V. & Klingenspor, M. *Biochim. Biophys. Acta* **1817**, 1660–1670 (2012).
11. Divakaruni, A. S., Humphrey, D. M. & Brand, M. D. *J. Biol. Chem.* **287**, 36845–36853 (2012).

The authors declare no competing interests.
This article was published online on 24 July 2023.