

receptor resembles the  $\alpha$ -coronavirus receptor APN and the SARS-CoV receptor ACE2. All three receptors are ectopeptidase enzymes that cleave amino acids from biologically active peptides, thereby regulating an array of physiological responses. However, APN, ACE2 and DPP4 do not share obvious structural features, and their peptidase activities are not necessary for virus entry<sup>7,8</sup>. Coronavirus adaptation to ectopeptidase receptors may, therefore, simply reflect the abundance or subcellular positioning of these enzymes on airway cells.

That said, once they have robustly infected a cell, viruses interfere with the presentation of such receptors at the cell surface, and decreased ACE2 levels during SARS-CoV infection are correlated with enhanced disease severity<sup>9</sup>. Further research to determine whether hCoV-EMC disease is similarly related to dysregulated DPP4-mediated physiological responses will address the intriguing hypothesis that aspects of coronavirus pathogenesis are outcomes of adaptation to ectopeptidase receptors.

Knowing the identity of the hCoV-EMC receptor will also allow the development of animal models of infection to assess whether there are causal links between DPP4 levels, hCoV-EMC infection and disease. For example, an evaluation of DPP4 distribution in the lungs will help to show whether the receptors' location restricts hCoV-EMC infections to the lower respiratory tract, which might limit the virus's transmissibility. DPP4 is found on non-ciliated airway cells, whereas ACE2 is expressed by ciliated cells (Fig. 1); such cell-target differences may contribute to the differences in transmissibility and pathogenicity of infections caused by hCoV-EMC and SARS-CoV. The potential for other factors — such as soluble DPP4, which may be abundant in extracellular fluids — to preclude infection and disease should also be tested. Moreover, DPP4 is known to have roles in recruiting protective immune responses in the host<sup>10</sup>; as such, the effects of virus-induced receptor dysregulation may feature prominently in elucidating immunopathological aspects of the disease.

Although hCoV-EMC can be transmitted from human to human, fortunately this seems to occur infrequently. Further epidemiological studies should assess whether the human infection is truly rare and always severe or, alternatively, is widespread but generally mild and therefore not detected. Similar epidemiological considerations apply to animals. Although the immediate implication of Raj and colleagues' findings might be to postulate a direct transmission from bats to humans, the conservation of the DPP4 receptor among species also raises questions about the extent of hCoV-EMC in nature and the most proximal animal source of the human infections. The interesting and perhaps troubling findings from studies of this virus thus far are

that there may be a plethora of sources for its intrusion into the human population. Is this the case, or are there distinct interspecies barriers to hCoV-EMC infection? If so, what is the nature of the barriers, and how might the virus adapt to cross them and occupy the human-host niche? Virus adaptations involve much more than evolving new receptor-binding domains and so, in further studies of this emergent pathogen, it will be important to consider other genetic determinants of hCoV-EMC transmission to humans, such as virus interactions with the innate immune system. ■

**Tom Gallagher** is in the Department of Microbiology and Immunology, Loyola University Medical Center, Maywood, Illinois 60153, USA. **Stanley Perlman** is in the

Department of Microbiology, University of Iowa, Iowa City, Iowa 52242, USA. e-mails: [tgallag@lumc.edu](mailto:tgallag@lumc.edu); [stanley-perlman@uiowa.edu](mailto:stanley-perlman@uiowa.edu)

1. Zaki, A. M., van Boheemen, S., Bestebroer, T. M., Osterhaus, A. D. & Fouchier, R. A. N. *Engl. J. Med.* **367**, 1814–1820 (2012).
2. Raj, V. S. et al. *Nature* **495**, 251–254 (2013).
3. Li, W. et al. *Science* **310**, 676–679 (2005).
4. Becker, M. M. et al. *Proc. Natl Acad. Sci. USA* **105**, 19944–19949 (2008).
5. van Boheemen, S. et al. *mBio* **3**, e00473-12 (2012).
6. Kindler, E. et al. *mBio* **4**, e00611-12 (2013).
7. Reguera, J. et al. *PLoS Pathogens* **8**, e1002859 (2012).
8. Li, F., Li, W., Farzan, M. & Harrison, S. C. *Science* **309**, 1864–1868 (2005).
9. Kuba, K. et al. *Nature Med.* **11**, 875–879 (2005).
10. Ansoorge, S. et al. *Clin. Chem. Lab. Med.* **47**, 253–261 (2009).

## EARTH SCIENCE

# Core composition revealed

**The composition of Earth's core may be easier to resolve than previously thought. Laboratory experiments strengthen the hypothesis that oxygen and silicon are the prime candidates for the light elements present in the outer core.**

LIDUNKA VOČADLO

**H**ow do you work out the composition of Earth's core when it lies 3,000–6,000 kilometres below your feet and is completely inaccessible? Writing in *Geophysical Research Letters*, Tsuno and colleagues<sup>1</sup> have tried to do just that by using a series of laboratory experiments to recreate the conditions expected during the formation of the core.

From studies involving seismology and cosmochemistry, we know that Earth's core consists predominantly of iron, alloyed with up to about 10% nickel. But the density of the core as measured from seismic-wave velocities is significantly lower (by 10–15%) than that of a pure metal alloy, and therefore the core must also contain some light elements. In a dynamic process, the solid inner core is crystallizing out of the liquid outer core, preferentially expelling light elements into the outer core. The inner core contains about 3% light elements, whereas the outer core contains nearer 10%. Cosmochemical and other arguments suggest that obvious candidates for these light elements include sulphur, silicon, oxygen and carbon, and these elements (and others) have been studied extensively for the past 20 years or so. But none of these light elements seems to satisfy all the requirements imposed by seismology, cosmochemistry and the evolutionary

models describing how Earth has evolved over time.

Given that the liquid outer core is surrounded by a silicate lower mantle, it is not surprising that silicon and/or oxygen are prime candidates for the light elements in the outer core. Also, a few per cent silicon hidden in the core conveniently accounts for the observation that silicon is slightly lower in the silicate part of Earth than in chondritic meteorites, which are thought to reflect the primordial composition of the whole Earth.

Further support for silicon and/or oxygen comes from arguments based on volatility data that tend to reject the more volatile carbon and sulphur (among others) in favour of silicon. In the case of oxygen, however, there has been a problem, because geochemical models of Earth's early evolution suggested that the core could only have formed with little or no oxygen<sup>2</sup>. However, a recent study<sup>3</sup> indicates that, conversely, the core could actually have formed under oxidizing conditions, thereby making oxygen a viable candidate for a light element in the core after all.

But having only silicon or only oxygen in the outer core is not sufficient to explain the core's composition. A theoretical study<sup>4</sup> has shown that, at the pressure and temperature conditions of the present-day boundary between Earth's inner and outer cores (a pressure of 330 billion pascals and an estimated

temperature of up to 6,000 kelvin), silicon is equally able to be present in the solid inner core and the liquid outer core. Thus, silicon will not produce the marked change in density that is observed from seismology studies of the boundary between the solid and liquid core. By contrast, oxygen can exist only in the liquid outer core, and thus will produce a density jump at this boundary. Therefore, to obtain the required reductions in density for both the inner and outer cores, together with the density jump across the boundary between them, both of these elements seem to be necessary.

Nonetheless, having oxygen and silicon together in the core poses another problem. When experimentalists try to put oxygen and silicon into liquid iron, their results indicate that these elements seem to be mutually exclusive — in fact, in the steel industry, silicon has been used as a deoxygenating agent. Furthermore, this incompatibility has been found to persist at the high pressures (40–60 GPa) and temperatures (less than about 3,000 K) expected during core formation in the early stages of Earth's evolution.

Tsuno and colleagues' work may have provided a solution to this problem of core composition. The authors performed experiments at a pressure of 25 GPa and a temperature of about 3,000 K on samples consisting of a liquid iron-rich metal interfaced with liquid silicate. The samples also included iron oxide, as this is particularly important in controlling the way in which silicon and oxygen partition between the silicate and the metal. They then determined the distribution of silicon and oxygen between the silicate and the metal alloy, and used the results to develop a thermodynamic model of the system. This model predicts that, when the temperature is increased by only a few hundred degrees (from 3,000 K to 3,500 K), the amounts of silicon and oxygen present in liquid iron increase to well above those required to match the density deficit inferred from seismic-wave data. Although the conclusions from this work have been suggested before<sup>5</sup>, it is the incorporation of iron oxide, which controls the availability of oxygen in the experiments, that makes the authors' conclusions more definitive.

However, it is worth noting that Tsuno and colleagues' experiments were performed at relatively modest temperatures (about 3,000 K), and so their conclusion that silicon is more readily incorporated into liquid iron alloyed with oxygen at 3,500 K is based on an extrapolation of their data. This will need to be tested. Moreover, a requirement for oxygen and silicon to be the light elements in the core is that this iron–oxygen–silicon alloy is then able to match the observed seismic-wave velocities and the density of the present-day core. The relevant physical properties of the alloy, however, are not yet known at the temperatures and pressures of the present-day core.

Finally, the samples used here contained no nickel and, at the temperatures of these experiments, nickel may not be as iron-like (that is, have similar physical and chemical properties) as previously thought<sup>6</sup>. Nevertheless, the arguments for a combination of oxygen and silicon as being the light elements in the core have now been significantly strengthened. Perhaps the most likely and most abundant elements do provide the real solution after all. ■

Lidunka Vočadlo is in the Department of Earth Sciences, University College London,

London WC1E 6BT, UK.  
e-mail: l.vocadlo@ucl.ac.uk

1. Tsuno, K., Frost, D. J. & Rubie, D. C. *Geophys. Res. Lett.* **40**, 66–71 (2013).
2. Wood, B. J., Walter, M. J. & Wade, J. *Nature* **441**, 825–833 (2006).
3. Siebert, J., Badro, J., Antonangeli, D. & Ryerson, F. J. *Science* <http://dx.doi.org/10.1126/science.1227923> (2013).
4. Alfè, D., Gillan, M. J. & Price, G. D. *Earth Planet. Sci. Lett.* **195**, 91–98 (2002).
5. Takafuji, N., Hirose, K., Mitome, M. & Bando, Y. *Geophys. Res. Lett.* **32**, L06313 (2005).
6. Martorell, B., Brodholt, J., Wood, I. G. & Vočadlo, L. *Earth Planet. Sci. Lett.* **365**, 143–151 (2013).

## CELL BIOLOGY

# Alternative energy for neuronal motors

**Neurons use molecular motors to power the transport of cargoes along their axonal extensions. Fresh evidence challenges the view that cellular organelles called mitochondria are the main energy providers for this process.**

GIAMPIETRO SCHIAVO & MIKE FAINZILBER

Intracellular transport requires energy, and nowhere is this process more energy-demanding than in the axon of a neuron. The length of an axon can range from millimetres in flies to metres in large mammals — a prodigious distance for the molecular motors that travel back and forth conveying cellular cargoes between the neuronal cell body and the nerve endings. These motors move along microtubules in discrete steps of a few nanometres each, and every step requires energy that the motors derive from the hydrolysis of ATP molecules. Consequently, axonal transport consumes large amounts of ATP, and organelles called mitochondria are widely assumed to be the principal source of this energy. But in a paper published in *Cell*, Zala *et al.*<sup>1</sup> challenge this assumption, showing that a sugar-hydrolysing enzyme bound to the surface of transport vesicles provides the energy for this process. In other words, motor complexes in axons seem to use on-board 'generators' to ensure a steady energy supply en route to their destination.

Mitochondria regulate their mobility according to the intracellular levels of calcium ions that accumulate in the axon at specialized energy-requiring sites rich in ion channels<sup>2</sup>. The distance between adjacent clusters of mitochondrial-ATP gradients<sup>3</sup>. Zala *et al.* therefore set out to identify the energy source for transport in axonal regions that lack mitochondria. Surprisingly, inhibition of mitochondrial ATP production did not significantly affect the axonal

transport of vesicles carrying the growth factor BDNF, regardless of the apparent ATP levels in the axon.

Cells can generate energy independently of mitochondria by breaking down sugars using a process called glycolysis. Unexpectedly, Zala and colleagues found that chemical inhibition of the key glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), or reduction in its expression, blocked the transport of axonal vesicles. GAPDH was present on the surface of these transport vesicles (Fig. 1), where it was bound by huntingtin — a motor-associated protein that is mutated in the neurodegenerative disorder Huntington's disease<sup>4</sup>. These findings have strong parallels with earlier work<sup>5</sup> demonstrating a role for GAPDH, but not mitochondria, in the bioenergetics of the uptake of neurotransmitter molecules into synaptic vesicles at nerve endings. The two studies add localized energy provision to the growing list of diverse functions of GAPDH in different subcellular compartments<sup>6</sup>.

Zala and co-authors' work might also have therapeutic implications. Their results indicate that mitochondrial impairment is unlikely to be the main cause of the alterations in fast axonal transport seen in neurodegenerative disorders such as Huntington's disease and amyotrophic lateral sclerosis (ALS). This could explain the failure of previous efforts<sup>7</sup> to ameliorate disease in a mouse model of ALS by increasing mitochondrial mobility. Furthermore, the affinity of GAPDH for aggregating proteins found in various neurodegenerative disorders<sup>8</sup> indicates that sequestration of this enzyme away from transport vesicles