synthesis of such 'cage' molecules is challenging, and the resulting compounds can turn out to be solids, or liquids that are too viscous for most applications.

Another way to produce porous liquids is to dissolve cage molecules in solvents that consist of bulky molecules (or in ionic liquids that consist of bulky ion pairs), so that the solvent cannot enter the cages[3]. Taking this idea further, porous liquids have also been prepared by dispersing porous solids in liquids whose molecules are too large to enter the pores[4]. This strategy has opened up countless opportunities for preparing porous fluids based on ionic liquids[5] and other organic solvents that have bulky molecules[6], with potential applications in any area that uses liquid solvents. The design of a porous liquid therefore comes down to choosing a porous solid and an appropriate bulky liquid – the choices made determine the properties of the final material.

However, this strategy cannot be used to prepare porous water, because almost all the cavities in porous solids are large enough to accommodate water molecules. Erdosy *et al.* therefore used a different approach. They were inspired by biomolecules with cavities that are big enough to host water, but which remain empty because hydrophobic groups in the pores repel water molecules. The authors decided to disperse hydrophobic porous solids in water to form stable dispersions (colloidal suspensions) that act as porous liquids. Their hypothesis was that the low affinity of water molecules for the pores would be sufficient to maintain voids in the aqueous suspension (Fig. 1).

Erdosy and colleagues did indeed obtain stable suspensions using uniformly sized nanocrystals of a hydrophobic porous solid known as silicalite-1 (a member of the zeolite family of porous solids, which are widely used in industrial applications). The authors also obtained stable colloidal suspensions using ZIF-8 and ZIF-67 – which belong to a group of porous solids known as zeolitic imidazolate frameworks (ZIFs). The ZIF compounds required their external surfaces to be modified by the non-covalent association of water-soluble proteins, or by the covalent attachment of small organic ligand molecules, to stabilize the suspensions.

The authors found that their colloids have a lower density than that of pure liquid water, indicating that the pores in the solids do not fill with water molecules in the aqueous suspensions. Further proof of this was obtained from molecular simulations, which showed that water molecules forced into the pores are spontaneously expelled. Moreover, the simulations showed that oxygen is rapidly adsorbed from aqueous solution by the suspended porous solids.

Erdosy *et al.* report that oxygen can be reversibly adsorbed by porous water prepared using only 4.0% by volume of silicalite-1 nanocrystals (90 nanometres in size), reaching oxygen levels higher than that of blood. When the concentration of porous solid is increased to 12.7% by volume, the oxygen-carrying capacity increases to values similar to the density of pure oxygen gas. The porosity of the suspensions could be increased still further using the hydrophobic zeolite ZSM-5. This forms stable colloids at concentrations as high as 40% by volume – and has an extremely high oxygen-carrying capacity that, to the best of the authors' knowledge, far exceeds the capacity of any other aqueous oxygen carriers.

"The pores in the solids do not fill with water molecules in the aqueous suspensions."

Not all porous aqueous fluids could be used for sustainable applications that require high gas concentrations. Many factors, other than gas capacities, have to be taken into account when designing porous water for a given application. For example, the stability of the suspensions could affect their use in energy storage devices, and the toxicity of the porous solids needs to be considered in medical oxygenating fluids. But given that myriad solids with hydrophobic pores could be designed to be biocompatible and sustainable, I am confident that stable aqueous colloidal suspensions will be used to considerably improve any technology that requires large concentrations of gases in water.

Porous water could, in principle, be used in blood substitutes, and to replace polluting organic solvents that have high gas capacities in the high-throughput synthesis of chemicals, in gas separations and in the capture and use of CO_2. It could also help to lower the energy demands of many chemical processes, because it would enable high gas concentrations to be attained in water under ambient conditions. It seems that porous water is here to stay.

Margarida Costa Gomes is in the Chemistry Laboratory, École Normale Supérieure de Lyon, 69364 Lyon, France.
e-mail: margarida.costa-gomes@ens-lyon.fr

1. Erdosy, D. P. *et al. Nature* **608**, 712–718 (2022).
2. O'Reilly, N., Giri, N. & James, S. L. *Chem. Eur. J.* **13**, 3020–3025 (2007).
3. Giri, N. *et al. Nature* **527**, 216–220 (2015).
4. Jie, K., Zhou, Y., Ryan, H. P., Dai, S. & Nitschke, J. R. *Adv. Mater.* **33**, 2005745 (2021).
5. Costa Gomes, M., Pison, L., Červinka, C. & Padua, A. *Angew. Chem. Int. Edn* **57**, 11909–11912 (2018).
6. Cahir, J. *et al. Chem. Sci.* **11**, 2077–2084 (2020).

The author declares no competing interests.

Metabolism

Long-sought mediator of vitamin K recycling

Nathan P. Ward & Gina M. DeNicola

The identity of the enzyme that enables vitamin K to combat the adverse side effects of a drug called warfarin has been long sought. Analysis of a type of cell death called ferroptosis has now unexpectedly solved the mystery. **See p.778**

Vitamin K was discovered by the biochemist Henrik Dam in 1936, and named after its role in promoting blood clotting, or *koagulation*, in Dam's native Danish[1]. The vitamin is a type of molecule called a naphthoquinone. It can exist in multiple forms, but only one supports clotting – the 'reduced hydroquinone' form, known as VKH2. Levels of VKH2 are maintained in the body by the enzyme vitamin K epoxide reductase (VKOR), which is part of the major (canonical) vitamin K recycling pathway. On page 778, Mishima *et al.*[2] pin down the identity of a different reductase enzyme that has a role in another crucial vitamin K recycling pathway.

When blood clotting needs to be treated – for example, in response to a stroke – the anticoagulant warfarin is used to inhibit VKOR, thus lowering levels of clot-promoting VKH2 in the blood (Fig. 1a). Although effective, warfarin therapy can easily lead to warfarin poisoning[3], in which life-threatening bleeding arises owing to a lack of clotting. The standard clinical treatment for warfarin poisoning is administration of a high dose of vitamin K, which is reduced to VKH2 by a warfarin-resistant reductase, thereby enabling clotting[3]. Until now, the identity of this 'non-canonical' reductase has been unknown.

The group that performed the current study was already familiar with one candidate reductase, the enzyme FSP1. The researchers had previously shown FSP1 to be a suppressor

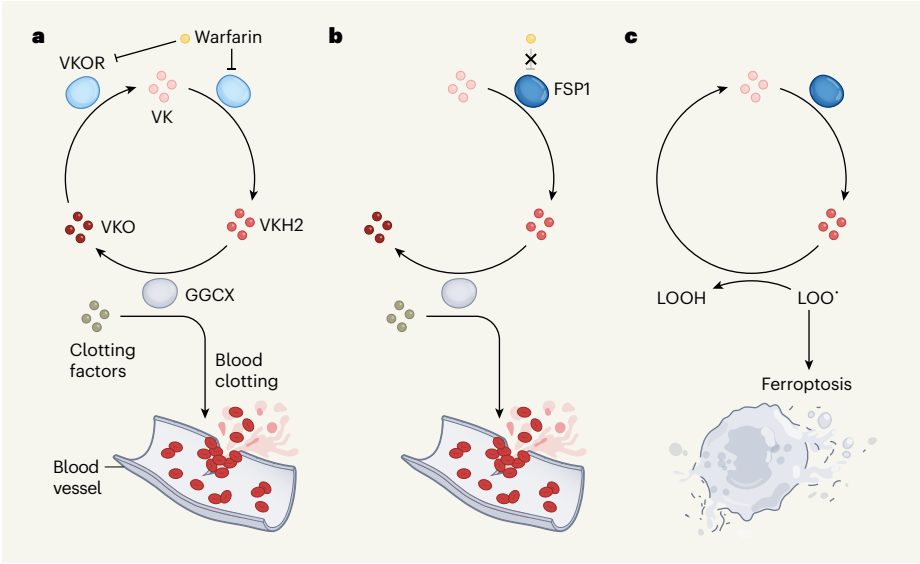

Figure 1 | Vitamin K recycling. a, In the body, ingested vitamin K (VK) is reduced by the enzyme vitamin K epoxide reductase (VKOR) to produce a reduced hydroquinone form of vitamin K, VKH2. This form of vitamin K acts as a cofactor for the enzyme γ-glutamyl carboxylase (GGCX), which modifies several clotting factors to promote blood clotting, generating vitamin K epoxide (VKO) from VKH2 as a by-product. It can then be recycled back to VK in steps that also involve VKOR. The drug warfarin inhibits VKOR, blocking the cycle to prevent blood clotting. **b**, Mishima *et al.*[2] report that the enzyme FSP1 can also reduce VK to promote clotting, but is not inhibited by warfarin. **c**, They also find that VKH2 produced through this pathway eliminates radicals called lipid peroxyl radicals (LOO•), which promote a type of cell death known as ferroptosis. The interaction produces intermediates called lipid hydroperoxides (LOOH) and recycles VKH2 back to VK.

of ferroptosis[4] – a form of cell death triggered when lipids are damaged by radicals to form lipid peroxides. The group had demonstrated that FSP1 eliminates lipid radicals from cells using the molecule ubiquinone (CoQ10) as a substrate. In the current study, Mishima *et al.* investigated whether FSP1 could also reduce vitamin K, which shares structural similarities with CoQ10.

Indeed, the authors found that FSP1 reduces vitamin K and is insensitive to warfarin. Fsp1 was necessary to protect against lethal brain haemorrhage in mice that had warfarin poisoning and received high-dose vitamin K treatment. Moreover, warfarin-treated human cells had only a minimal capacity to reduce vitamin K levels if they lacked FSP1. Thus, FSP1 is the long-sought mediator of non-canonical vitamin K reduction (Fig. 1b).

This finding indicates that FSP1 should be a consideration when managing thrombosis and other clotting disorders. Genetic variants in the gene that encodes FSP1 have been identified in people[5,6], but their effect on FSP1 function has not been characterized. Variation in FSP1 activity across the human population could reduce the effectiveness of warfarin in people for whom FSP1 is more active. By contrast, people who exhibit low FSP1 activity could require more vitamin K to combat warfarin poisoning. Future studies examining the interaction between an individual's FSP1 function, dietary vitamin K intake and warfarin sensitivity are warranted[7].

Next, Mishima *et al.* investigated whether vitamin K could also act as a substrate for FSP1-mediated peroxide detoxification. A second enzyme, glutathione peroxidase 4 (GPX4), also eliminates lipid peroxides, so the authors used a series of GPX4-deficient cell and mouse models to negate this pathway's influence in their experiments. Vitamin K is ingested in one of three forms – as naturally occurring phylloquinone (PK) or menaquinone (MK4), or as the synthetic variant menadione – and the authors found that all three could inhibit ferroptosis in GPX4-deficient cells. Importantly, FSP1 reductase activity was crucial for the anti-ferroptotic effect of vitamin K, both *in vitro* and *in vivo*. The authors demonstrated that FSP1 reduces vitamin K to VKH2, which acts as an antioxidant, mopping up radicals. This prevents lipid peroxidation and regenerates vitamin K (Fig. 1c).

"This finding indicates that the FSP1 protein should be a consideration when managing thrombosis and other clotting disorders."

Intriguingly, Mishima *et al.* discovered that the MK4 form of vitamin K is better at removing peroxides and suppressing ferroptosis than is CoQ10. Given that FSP1 can use both, an obvious next question is which is the preferred substrate *in vivo*? The authors did not examine this directly, but there are some clues from evolution. Vitamin K serves as a predominant electron carrier in bacteria and plants, whereas primordial oxygenation of the atmosphere seems to have selected for CoQ10 in animals, owing to its higher redox potential and abundance[8]. This information suggests that CoQ10 is probably the preferred substrate in animals *in vivo*, and that administration of high-dose vitamin K has the potential to suppress ferroptosis as a therapeutic strategy.

Ferroptosis causes considerable harm when blood supply is lost from a tissue[9] and subsequently restored – a damaging phenomenon called ischaemia–reperfusion injury (IRI). In a final set of experiments, Mishima *et al.* showed that vitamin K supplementation suppressed ferroptosis and prevented tissue-damaging inflammation in mice subjected to IRI in the liver or kidneys. Furthermore, vitamin K prevented ferroptosis in neurons, demonstrating its broad action across tissues. Although the focus of these studies was on the ferroptosis-suppressing activity of vitamin K in the context of FSP1, the results also raise the question of whether VKOR can promote ferroptosis suppression in certain contexts.

These findings suggest the exciting potential for using vitamin K supplementation as a potent means of warding off IRI in people at high risk of ischaemia – those who have cardiovascular disease, for instance. Vitamin K is well tolerated, and no toxicity is found with administration of the PK or MK4 forms for treating warfarin poisoning. However, it is administered as an acute dose, and the effects of long-term administration have not been determined. Clinical trials to test this application are now needed – and because vitamin K is already given to people, these could occur very soon.

Nathan P. Ward and **Gina M. DeNicola** are in the Department of Cancer Physiology, Moffitt Cancer Center, Tampa, Florida 33612, USA.
e-mail: gina.denicola@moffitt.org

1. Dam, H. & Schønheyder, F. *Biochem. J.* **30**, 897–901 (1936).
2. Mishima, E. *et al. Nature* **608**, 778–783 (2022).
3. Chiquette, E., Amato, M. G. & Bussey, H. I. *Arch. Intern. Med.* **158**, 1641–1647 (1998).
4. Doll, S. *et al. Nature* **575**, 693–698 (2019).
5. Barton, A. R., Sherman, M. A., Mukamel, R. E. & Loh, P.-R. *Nature Genet.* **53**, 1260–1269 (2021).
6. Ahola-Olli, A. V. *et al. Am. J. Hum. Genet.* **100**, 40–50 (2017).
7. Lurie, Y., Loebstein, R., Kurnik, D., Almog, S. & Halkin, H. *Br. J. Clin. Pharmacol.* **70**, 164–170 (2010).
8. Ilbert, M. & Bonnefoy, V. *Biochim. Biophys. Acta* **1827**, 161–175 (2013).
9. Jiang, X., Stockwell, B. R. & Conrad, M. *Nature Rev. Mol. Cell Biol.* **22**, 266–282 (2021).

The authors declare no competing interests.
This article was published online on 3 August 2022.