Dasenbrock-Gammon *et al.* obtained evidence for near-ambient superconductivity by replacing some of the hydrogen in a lutetium hydride compound with nitrogen, which increased the number of charge carriers. The authors fabricated the compound at a pressure of 2 GPa. They then lowered the pressure to 1 GPa and measured a superconducting phase with a maximum transition temperature of 294 K. This is the highest temperature recorded at such low pressures (Fig. 1).

The sample underwent a striking visual transformation as it transitioned through different phases with changing pressure. When the non-superconducting metal was compressed, its colour changed from blue to pink, coincident with the onset of the superconducting regime at 171 K and 0.5 GPa. Then, when the authors compressed the sample to more than 1 GPa, the sample became non-superconducting again and its colour changed to a vivid red. It is intriguing that the superconducting state appeared only in the pink phase marked by intermediate pressures.

Dasenbrock-Gammon *et al.* made various measurements to show that this phase was indeed superconducting. They measured electrical resistance, and looked at how the voltage across their sample depended on the current through it. They also measured the temperature dependence of magnetic susceptibility (how easily a sample can be magnetized) and of a thermodynamic quantity called specific heat.

These measurements were all consistent and comprehensive. However, the authors' discovery will no doubt be controversial, because researchers from the same team previously retracted a report[14] of high-temperature superconductivity in carbonaceous sulfur hydride[15]. Independent measurements of the material, its properties and fabrication process will help to assuage any doubts about the results.

The authors suggest that hydrogen's high vibration frequency and the extra charge carriers from the nitrogen both contribute to the high-temperature superconducting state they measured. To determine whether this is indeed the case, more needs to be known about the composition and structure of the material. Dasenbrock-Gammon *et al.* used a technique called X-ray diffraction to show that the lutetium formed a closely packed crystal lattice, in an arrangement known as a face-centred-cubic structure, in some of the phases they detected. However, the locations of the hydrogen and nitrogen atoms could not be detected with X-rays. Future work is required to understand their distribution, which could be measured, for example, using neutron-diffraction methods.

The concentrations of hydrogen and nitrogen are also unknown. Dasenbrock-Gammon and colleagues' structural model holds that the distance between hydrogen atoms is 2.19 ångströms. This is surprisingly large — almost twice that of other hydrides exhibiting high-temperature superconductivity[16–18] — and suggests that there is relatively little hydrogen present in the authors' samples compared with in similar superconducting compounds.

If the nitrogen doping is indeed partly responsible for the superconducting state, its role in achieving such a high transition temperature is yet to be determined. Further research will be needed to confirm that Dasenbrock-Gammon and co-workers' material is a high-temperature superconductor, and then to understand whether this state is driven by vibration-induced Cooper pairs — or by an unconventional mechanism that is yet to be uncovered.

Regardless of the mechanism, the prospect of a material that superconducts under ambient conditions is tantalizing. Superconducting materials make powerful magnets that are used, for example, in magnetic resonance imaging (MRI) — a technology that has had a profound impact on medical diagnostics since it first appeared half a century ago[19]. Such magnets can also be used to levitate objects, and this ability has inspired the idea of a high-speed train that would optimize energy consumption by minimizing friction.

But standard MRI systems currently require expensive refrigeration in the absence of high-temperature superconducting components. And trains that travel as fast as aircraft on a fraction of the power are still a thing of the future. Perhaps Dasenbrock-Gammon and colleagues' hydride compound will bring us a step closer to such technologies becoming a reality.

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1. Chu, C. W. *Physica C* **482**, 33–44 (2012).
2. Drozdov, A. P., Eremets, M. I., Troyan, I. A., Ksenofontov, V. & Shylin, S. I. *Nature* **525**, 73–76 (2015).
3. Dasenbrock-Gammon, N. *et al. Nature* **615**, 244–250 (2023).
4. Bardeen, J., Cooper, L. N. & Schrieffer, J. R. *Phys. Rev.* **108**, 1175–1204 (1957).
5. Ashcroft, N. W. *Phys. Rev. Lett.* **21**, 1748–1749 (1968).
6. McMahon, J. M., Morales, M. A., Pierleoni, C. & Ceperley, D. M. *Rev. Mod. Phys.* **84**, 1607–1653 (2012).
7. Ashcroft, N. W. *Phys. Rev. Lett.* **92**, 187002 (2004).
8. Drozdov, A. P. *et al. Nature* **569**, 528–531 (2019).
9. Somayazulu, M. *et al. Phys. Rev. Lett.* **122**, 027001 (2019).
10. Li, Z. *et al. Nature Commun.* **13**, 2863 (2022).
11. Ma, L. *et al. Phys. Rev. Lett.* **128**, 167001 (2022).
12. Keimer, B., Kivelson, S. A., Norman, M. R., Uchida, S. & Zaanen, J. *Nature* **518**, 179–186 (2015).
13. Ishida, K., Nakai, Y. & Hosono, H. *J. Phys. Soc. Jpn* **78**, 62001 (2009).
14. Snider, E. *et al. Nature* **586**, 373–377 (2020).
15. Snider, E. *et al. Nature* **610**, 804 (2022).
16. Duan, D. F. *et al. Sci. Rep.* **4**, 6968 (2014).
17. Peng, F. *et al. Phys. Rev. Lett.* **119**, 107001 (2017).
18. Wang, H., Tse, J. S., Tanaka, K., Iitaka, T. & Ma, Y. *Proc. Natl Acad. Sci. USA* **109**, 6463–6466 (2012).
19. Lauterbur, P. C. *Nature* **242**, 190–191 (1973).
20. Gao, G. *et al. Mater. Today Phys.* **21**, 100546 (2021).

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Plant sciences

A protein entry path into chloroplasts

Takashi Hirashima & Toshiya Endo

Structures of the machinery for importing proteins into chloroplast organelles of algae, determined using cryo-electron microscopy, have opened a new chapter in efforts to understand how chloroplasts are built. **See p.349**

Chloroplasts are organelles, found in plants and algae, that house hundreds of different proteins responsible for photosynthesis, a process essential for life on Earth. Most chloroplast proteins are encoded by the nuclear genome, are made in the cytosol and contain a chloroplast-targeting signal. To be imported into the chloroplast, such proteins must cross the outer and inner envelope membranes (OEM and IEM, respectively) that surround the organelle. Protein complexes on the OEM (called TOC) and IEM (called TIC) form the intricate machinery that mediates protein transport across the two membranes[1–3]. On page 349, Liu *et al.*[4] report the cryo-electron microscopy (cryo-EM) structures of the TOC–TIC supercomplex from the unicellular green alga *Chlamydomonas reinhardtii*. This and another such structure reported in *Cell* by Jin *et al.*[5] are the first high-resolution structures of the TOC and TIC complexes — they provide surprises and insights, but also raise many questions.

Chloroplast-destined proteins are recognized and move from the cytosol across the OEM with the aid of the TOC complex. Previous

biochemical characterization of mainly plant chloroplasts indicates that the TOC complex contains two proteins, Toc34 and Toc159, which function as surface receptors for chloroplast-targeting signals, and the protein Toc75, which forms a structure called a β-barrel and is thought to be a protein-import channel.

The first surprise from the cryo-EM structures is that Toc75 assembles together with another protein, Toc90 (also known as Toc120), which is a *Chlamydomonas* version of the plant protein Toc159, to form a large hybrid transmembrane (TM) β-barrel in the OEM that provides a route for protein entry. This barrel has 30 β-strand segments, and one 'seam' on the side of the barrel is a tightly sealed antiparallel β-sheet, whereas the other seam is formed through weak hydrophobic side-chain contacts. This latter seam might function as a flexible 'lateral gate' to enable the transport of proteins that either insert into the OEM or are too large to fit in the central pore and resist being unfolded for entry into the channel[6].

Another peculiar and unexpected observation is that a green-alga-specific OEM protein, Ctap4 (also known as Toc39), forms a second membrane-embedded β-barrel, which is approximately 12 ångströms from the main part of the TOC complex. The role of this smaller barrel remains to be determined.

Chloroplast proteins that have moved through the TOC complex travel through the aqueous intermembrane space (IMS) and cross the IEM through the TIC complex. This occurs in cooperation with the import motor proteins of the AAA–ATPase protein complex and/or soluble chaperone proteins inside the chloroplast[7]. The import motor might exert a pulling force to drive protein entry; however, this motor was not identified as being associated with the TIC structure determined in the current studies.

A remarkable feature of the TOC–TIC supercomplex is that the TOC and TIC complexes form an interlocked architecture in the IMS, tightly integrating the two complexes (Fig. 1). In both chloroplasts and mitochondria (another organelle surrounded by two membranes), efficient protein entry across the outer and inner membranes requires a coordinated operation. In plant chloroplasts, the TOC and TIC complexes form a stable supercomplex only in the presence of translocating proteins and/or with the aid of the bridging protein Tic236 (ref. 8). However, a relatively stable TOC–TIC supercomplex forms in the absence of these proteins in *C. reinhardtii* chloroplasts[9]. The supercomplex is stable without translocating proteins, and whether it has a version of a bridging protein was unknown. The unveiled cryo-EM structures show that the chloroplast-encoded Tic214 protein and other Tic proteins co-fold to build a unique IMS structure and associate with the IMS domains of the TOC components. In addition, a segment of Tic214 extends even further to enter the TOC hybrid barrel from the IMS side. However, the way in which Tic214 – made inside the chloroplast – is incorporated into the intricate IMS structure is a mystery.

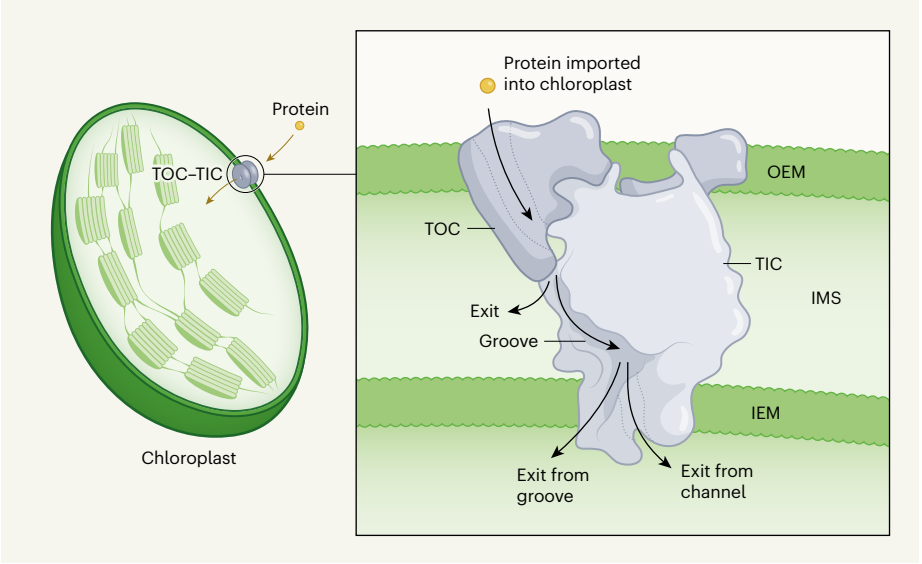

Figure 1 | The TOC–TIC supercomplex from an alga. Liu *et al.*[4] and Jin *et al.*[5] present structures, obtained using cryo-electron microscopy (cryo-EM), of this supercomplex, which is needed for protein entry into chloroplast organelles. The overall structure has components in the outer and inner envelope membrane (OEM and IEM, respectively) and in the intermembrane space (IMS). Some proposed routes for protein movement through a central channel or surface grooves are indicated. The papers differ regarding routes in the IEM-embedded TIC parts (the routes shown correspond to those proposed by Liu and colleagues).

The tight association of the TOC and TIC complexes would create a continuous protein-transport route from the cytosol all the way to inside the chloroplast. Such a route might prevent highly hydrophobic membrane proteins from forming misfolded aggregates in the IMS. However, it might also present a challenge for transporting some soluble proteins to the IMS. To overcome this problem, soluble IMS proteins might exit through the side openings of the TOC hybrid barrel towards the IMS, whereas proteins targeted to the interior of the chloroplast might be directed along the surface groove of the IMS architecture and then reach the protein-transport route in the membrane-embedded part of the TIC complex.

In contrast to the TOC complex, the membrane-embedded part of the TIC complex is organized with approximately 15 TM helices provided by Tic20, Tic214 and other Tic proteins. There is a long-standing debate about whether Tic20 and Tic110 have a central role in protein entry[3], and Tic110 was absent from the TIC structures. This raises the question of how protein entry is organized in the TIC complex. The answer is not clear, and different routes are proposed in the two papers. The TM helices from Tim20 and Tim214 collectively form a narrow conduit in the membrane-embedded portion of the TIC complex. Proteins could potentially move through this channel if it undergoes a conformational change to expand at the site of constriction. Alternatively, proteins might move along the surface groove of the TIC complex that faces the IEM.

In conjunction with mass spectrometry analyses[9], the cryo-EM structures of the TOC–TIC supercomplex have uncovered previously unknown components that are mostly specific to green algae. However, some potential components are missing from the cryo-EM structures, and the structures also contain segments that have yet to be identified. The components of the TOC–TIC systems, including their import motors, exhibit variation in their subunit composition during the development of plastids (organelles that can form structures such as chloroplasts), and have undergone changes during the evolution of algae and land plants, with the exception of their core components[3]. Therefore, gaining a deeper understanding of the precise functions of each component and obtaining high-resolution structures of the TOC–TIC system from land plants, as well as the TIC-associated motor complexes, will add more chapters to our understanding of chloroplast formation.

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1. Schleiff, E. & Becker, T. *Nature Rev. Mol. Cell Biol.* **12**, 48–59 (2011).
2. Jarvis, P. & López-Juez, E. *Nature Rev. Mol. Cell Biol.* **14**, 787–802 (2013).
3. Nakai, M. *Biochim. Biophys. Acta Bioenerg.*

1847, 957–967 (2015).
4. Liu, H., Li, A., Rochaix, J.-D. & Liu, Z. *Nature* **615**, 349–357 (2023).
5. Jin, Z. *et al. Cell* **185**, 4788–4800 (2022).
6. Ganesan, I., Shi, L.-X, Labs, M. & Theg, S. M. *Plant Cell* **30**, 2161–2173 (2018).
7. Kikuchi, S. *et al. Plant Cell* **30**, 2677–2703 (2018).
8. Chen, Y.-L. *et al. Nature* **564**, 125–129 (2018).
9. Ramundo, S. *et al. Proc. Natl Acad. Sci. USA* **117**, 32739–32749 (2020).

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Cancer

Fatty acids prime the lung as a site for tumour spread

Laura V. Pinheiro & Kathryn E. Wellen

The mechanisms that enable the deadly spread of cancer are not fully understood. It emerges that tumours can signal to the lung to manipulate lipids and so prime the organ to support tumour cells that subsequently spread there.

Cancer cells require nutrients such as glucose, amino acids and fatty acids to grow and proliferate. They also require nutrients to disperse and grow in organs distant from the initial (primary) tumour site — a spreading process called metastasis. The nutritional environment affects whether cancer cells can thrive in a new location. Tumour cells are known to secrete factors that act on distant sites ahead of their arrival, to prepare a favourable environment, termed a pre-metastatic niche[1]. However, nutritional aspects of the pre-metastatic niche are poorly understood. Writing in *Nature Cancer*, Altea-Manzano *et al.*[2] reveal how breast cancer cells program the metabolic environment in the lung before colonization, to support metastatic growth.

Fatty acids are a class of nutrient implicated in supporting metastasis, and high-fat diets promote metastasis in mice[3,4]. However, the factors that affect fatty-acid availability at sites of metastasis are not well known. Altea-Manzano *et al.* find that two fatty acids in particular, palmitate and oleate, are highly abundant in the extracellular fluid of the healthy lung and liver — common sites of metastasis. Feeding mice a high-fat diet further increases the fatty-acid abundance in these tissues, and coincides with increased metastatic growth in a breast cancer model.

The authors then considered a crucial question. Could tumour-derived signals remodel the metabolic environment of distant tissues to improve the ability of cancer cells to grow there? The researchers tested this by injecting mice with factors secreted by tumours *in vitro*. Remarkably, this treatment resulted in a rise in palmitate in the lung extracellular fluid, indicating that signals from a distant tumour can change the nutritional environment in the lung. Lung extracellular fluid collected post-mortem from people with breast cancer had higher levels of palmitate than that of individuals who had not had cancer, supporting the relevance of these findings for humans.

A cell type called a lung-resident alveolar type II (AT2) cell was identified as the source of palmitate-containing lipids (Fig. 1a). AT2 cells produce lung surfactant, a complex of phospholipids and proteins that functions to reduce surface tension at the air–liquid interface in the lung's alveolar structures, preventing their collapse. Surfactant is rich in lipids, suggesting that tumours might exploit the normal metabolic function of the AT2 cells.

To understand how palmitate gives metastasizing cancer cells an advantage, Altea-Manzano *et al.* used an experimental system to model features of tumours *in vivo* and to mimic 3D tumour growth. The set-up consisted of a culture system in which cells aggregate and grow into sphere-like structures[5]. Palmitate, but no other fatty acids tested, increased spheroid growth in a manner that required lipid breakdown to generate the metabolic intermediate acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is needed for a protein modification called acetylation, which can regulate protein function, and the abundance of acetyl-CoA can affect the acetylation of certain proteins, including some that are involved in regulating gene expression[6].

Altea-Manzano and colleagues found that acetyl-CoA derived from palmitate is used by an enzyme called KAT2A to acetylate subunit p65 of the transcription-factor protein NF-κB. This acetylation leads to increased expression of genes that promote metastasis. Although several nutrient sources can supply acetyl-CoA, palmitate, but no other nutrients tested, increased the expression of KAT2A, possibly accounting for the role of palmitate, but not other fatty acids, in this setting.

Targeting various components of this pathway in the cancer cells, including palmitate breakdown and KAT2A, potently suppressed spheroid growth in culture and tumour metastasis in mice. These findings delineate a mechanism whereby signals from the tumour instruct AT2 cells to produce and secrete lipids, increasing palmitate abundance in the pre-metastatic niche (Fig. 1b). Palmitate is then taken up by the metastasizing cancer

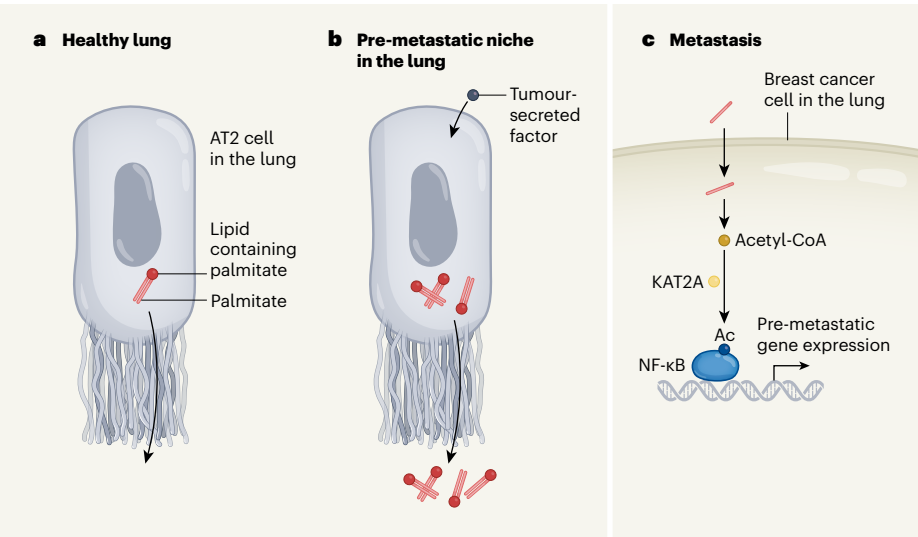

Figure 1 | Tumours manipulate lipids to create a favourable environment for tumour spread. Altea-Manzano *et al.*[2] investigated how breast cancer cells spread to the lungs in mice. **a**, AT2 cells in the lungs synthesize and secrete lipid molecules that contain the fatty acid palmitate. **b**, The authors report that unknown tumour-secreted factors boost palmitate production. This creates a favourable site for tumour spread (termed a pre-metastatic niche). **c**, When breast cancer cells themselves reach the lungs (through a process called metastasis), they take up palmitate and convert it to acetyl-CoA. This molecule is used by the enzyme KAT2A to add an acetyl group (Ac) to the transcription-factor protein NF-κB. NF-κB regulates gene expression to support tumour growth.