Fourier filtering, to produce images of most of the platinum nanoparticle, which has a volume of approximately 850 cubic nanometres. The authors have proved the existence of atom-size steps at the boundaries between regions known as twins inside the nanoparticle (these twins comprise regions in which the atomic ordering within each twin is perfect but the twins themselves differ from each other in their local atomic arrangements). In addition, they have produced what I believe are the first images of the 3D atomic structure right at the core of two types of well-known dislocation — edge and screw dislocations — in the nanoparticle. Many of us remember materials-science lectures and textbooks in which we saw classical 3D block images of an edge or a screw dislocation (Fig. 1), but it is remarkable to see this realized for individual atoms (see Figs 3 and 4 of the paper[1]).

Looking to the future, of particular interest for this 3D Fourier electron-tomography technique would be the development of a capability to map the exact location of every atom in a crystal. This is achievable to some extent in macromolecular or protein crystallography, although in these situations researchers have a priori knowledge of the molecular peptide sequence and stereochemistry, which helps greatly in refining the atomic positional modelling. The extension of 3D Fourier electron tomography to structures larger than nanoparticles should also be possible in principle, because the technique seems to be mainly constrained by electron scattering, and so imaging should depend chiefly on the electron-beam energy and the composition of the material under test. ■

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CANCER

A metabolic metamorphosis

Mutations in the enzyme isocitrate dehydrogenase lead to the accumulation of a metabolite that seems to promote cancer by influencing the epigenetic status of cells. But the effects are reversible, hinting at therapeutic targets.

ABIGAIL S. KRALL & HEATHER R. CHRISTOFK

The discovery of cancer-associated mutations in metabolic enzymes has fuelled the idea that altered cellular metabolism may be involved in the development of cancer. For example, mutations in isocitrate dehydrogenases 1 and 2 are commonly detected in brain tumours and leukaemia. These mutations cause the enzymes to produce the (*R*)-enantiomer of a metabolite called 2-hydroxyglutarate, which can accumulate in tissues[1,2]. Writing in *Science*, Losman *et al.*[3] now show that the presence of this metabolite alone can promote cancer-like properties in cells. Notably, they also demonstrate that its cancer-promoting effects are reversible, suggesting that therapies targeting isocitrate-dehydrogenase mutants might improve patient prognoses.

Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) function in the cytoplasm and in the citric-acid cycle, respectively, to convert isocitrate to α-ketoglutarate (Fig. 1). More than 75% of brain tumours and around 20% of acute myeloid leukaemias harbour mutations in IDH1 or IDH2[4,5] that confer on the enzymes the gain-of-function ability to convert α-ketoglutarate to (*R*)-2-hydroxyglutarate ((*R*)-2HG)[1,2], which suggests that these mutations transform cells in ways that contribute to tumour development.

Losman and colleagues tested this idea by expressing a cancer-associated mutant version of IDH1 in immature red blood cells. They observed that the cells were able to grow in the absence of certain, usually essential, growth factors, and that their differentiation into mature cells was impaired — two hallmarks of leukaemic cells. Moreover, the addition of cell-membrane-permeable (*R*)-2HG to cells without an IDH mutation had the same effects, indicating that this metabolite is the transforming agent — a bona fide 'oncometabolite'.

Dioxygenase enzymes that use α-ketoglutarate as a cofactor function in diverse cellular processes, such as adaptation to low oxygen levels or epigenetic modifications (alterations, such as methylation, to DNA or associated histone proteins that regulate gene expression without changing the DNA sequence). (*R*)-2HG, which structurally resembles α-ketoglutarate, promotes the activity of some of these enzymes by substituting for α-ketoglutarate[6], and inhibits others by competing with α-ketoglutarate for active-site binding[7]. For example, (*R*)-2HG inhibits the dioxygenase TET2 (ref. 7), whose activity leads to reduced DNA methylation. It also inhibits some histone demethylase enzymes, such as KDM enzymes[7,8]. Inhibition of these epigenetic modifiers results in DNA and histone 'hypermethylation signatures' that can alter gene expression to block cellular differentiation[9–11]. IDH mutations are therefore thought to promote cancer by modifying the epigenome to maintain cells in a stem-cell-like state.

In a series of compelling experiments, Losman *et al.* provide evidence that (*R*)-2HG transforms cells by inhibiting the activity of TET2. They find that blocking TET2 activity in cells recapitulated (*R*)-2HG-mediated growth-factor independence and impaired differentiation, reinforcing the suggestion that TET2 inhibition and the resulting epigenetic changes contribute to (*R*)-2HG-induced transformation.

However, the authors also identify one α-ketoglutarate-dependent dioxygenase whose activity must be maintained for (*R*)-2HG-mediated leukaemic transformation. This is EGLN, an enzyme that marks the transcription factor HIF-α for degradation (Fig. 1). This piece of the puzzle was elucidated when Losman *et al.* observed that the (*S*)-enantiomer of 2-hydroxyglutarate, (*S*)-2HG, does not promote leukaemia development, even though it inhibits TET2 and histone demethylases more potently than does (*R*)-2HG[6,7]. Therefore, it seemed probable that (*R*)-2HG promotes cellular transformation by modulating the activity of another dioxygenase.

It was recently demonstrated that (*R*)-2HG activates EGLN, whereas (*S*)-2HG inhibits it[6]. Consequently, Losman *et al.* reasoned that leukaemic transformation resulting from mutant IDH or (*R*)-2HG might require EGLN activity. Confirming this hypothesis, they observed that decreasing EGLN expression blocked transformation by mutant IDH or TET2 loss. Although the authors show that TET2 inhibition is sufficient for transformation and that EGLN activity is necessary for (*R*)-2HG-mediated transformation, whether TET2 inhibition is necessary for transformation by (*R*)-2HG remains to be tested.

The dependence of mutant IDH on EGLN activity during leukaemia development is surprising, as it contradicts the traditional view

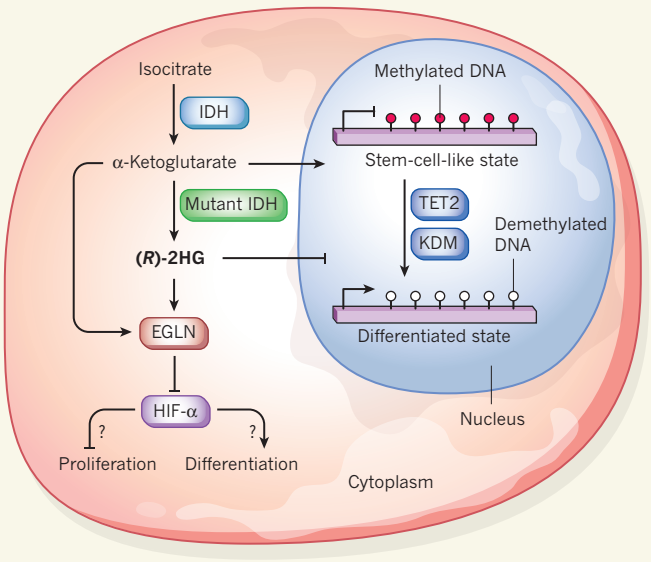

Figure 1 | An oncogenic metabolite. Mutations in the metabolic enzyme isocitrate dehydrogenase (IDH), which converts isocitrate to α-ketoglutarate can lead to accumulation of the normally irrelevant metabolite (*R*)-2HG. Losman *et al.*[3] show that the presence of (*R*)-2HG causes cells to become independent of growth factors and to lose the ability to progress from a stem-cell-like progenitor to a fully differentiated state — two hallmarks of leukaemic cells. The authors' data suggest that this occurs because the metabolite impairs the activity of α-ketoglutarate-dependent enzymes such as TET2 and KDM, which promote differentiation by removing methyl groups from DNA and DNA-associated histone proteins to alter gene expression. The authors also show that (*R*)-2HG-mediated cellular changes depend on the activity of EGLN, another enzyme that uses α-ketoglutarate as a cofactor. EGLN marks the transcription factor HIF-α for degradation. However, HIF-α is typically associated with cancer promotion, so the role of EGLN in (*R*)-2HG-mediated cancer promotion remains unclear.

of HIF-1α as a cancer-promoting protein. However, in support of Losman and colleagues' findings, previous studies have shown that HIF-1α can inhibit leukaemic-cell proliferation and induce the differentiation of myeloid cells[12]. This occurs in the absence of its typical transcription-factor partner HIF-1β, and seems to depend instead on CEBPα, a transcription factor that is crucial for blood-cell differentiation[13]. Further studies are needed to determine whether HIF-α loss is a major factor in (*R*)-2HG-mediated transformation.

Importantly, Losman *et al.* also demonstrate that the oncogenic effects of (*R*)-2HG are reversible — its removal restored the growth-factor dependence and differentiation capacity of cells even after long-term exposure to the metabolite. This reversibility is a key observation because mutant IDH may transform cells by altering the epigenome. The stable, inheritable nature of epigenetic modifications had raised concerns that targeting mutant IDH would not be therapeutically effective. But if (*R*)-2HG removal also results in reversion of hypermethylation signatures, this would indicate that the epigenetic modifications relevant to mutant IDH-mediated transformation are more dynamic than previously thought. Alternatively, however, the features of transformed cells may arise from atypical functions of epigenetic modifiers such as TET2, or solely from the activities of other enzymes affected by (*R*)-2HG, such as EGLN.

Mounting evidence suggests that metabolism and cellular epigenetic states are interconnected: because many epigenetic modifiers depend on metabolites as cofactors or substrates, the cell's metabolic state can influence its epigenetic state. Moreover, epigenetic modifications regulate many cellular processes central to cancer development. The study by Losman *et al.* bridges the fields of cancer, metabolism and epigenetics by showing that a metabolite that results from a genetic abnormality can promote cancer, possibly by changing the epigenetic landscape of the cell to alter gene expression. Continued study of the dynamic interplay between metabolism and epigenetics in cancer should lead to improved understanding of disease development and better therapeutic options. ■

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MATERIALS SCIENCE

The same, but better

Moving beyond mimicry, biologically inspired artificial materials can be simpler in design yet more powerful in function than their natural analogues. A tropical fruit seed serves as a guide to making new photonic elements.

TERI W. ODOM

Nature's bounty has provided the inspiration for a wide range of man-made photonic materials. For example, opals have given rise to artificial crystals made of colloidal building blocks[1], and the starfish-related brittlestar has shown how microlenses can act like a compound eye[2]. Now, as Kolle *et al.* report[3] in *Advanced Materials*, tropical plant seeds can be added to the list, and with them, a new biologically inspired photonic element — the soft optical fibre. The seeds of the rainforest plant *Margaritaria nobilis* look blue–green because of the way in which light interacts with the cells in the plant's seed coat, which are elongated, with a cross-section rather like a Swiss roll in structure (Fig. 1a,b). This hierarchical architecture, in which the overall curvature of the cell is microscale and the concentric features within the cell are nanoscale, provided the guiding principles for the authors' design of a multilayered photonic fibre (Fig. 1c).

What is significant about Kolle and colleagues' work is that they did not simply mimic the cellular structure of the coat, and hence obtain similar blue–green colours. Instead, they created a structure that had a simpler geometry which could not only produce blue and green colours, but also generate tunable colours over the visible spectrum. The key to this greater flexibility resides in the use of soft materials and in the fabrication method.

The colours of the seed coat are determined by the thickness and refractive index of the two alternating materials of the Swiss-roll structure, whereas the brightness is controlled primarily by the number of bilayers in the roll. When light shines on a multilayered stack of two alternating materials, the reflected colour — whose frequency falls within a range of 'forbidden' frequencies called the photonic bandgap — is preserved only at angles perpendicular to the surface. But because the cells in the seed coat have microscale curvature in addition to the concentric nanoscale multilayers, and the fruit itself has macroscale curvature, the blue–green colours can be observed over a wider range of angles.

To create a bilayer with different refractive indices, Kolle *et al.* used two polymers, polydimethylsiloxane (PDMS) and polystyrene–polyisoprene triblock copolymer (PSPI). The thicknesses of the two polymer layers determined the central frequency of the photonic bandgap. For example, a PDMS film 240 nanometres thick and a PSPI 100 nm thick that were rolled around a 14-micrometre-diameter glass rod nearly 80 times resulted in a green fibre (Fig. 1d). With its circular cross-section, this soft fibre could reflect green colour without needing the structural complexities of the seed coat, such as the cells' elliptical cross-section and the fine structure within their nanoscale layers.

Kolle *et al.* took advantage of the elastic properties of the polymer layers to tune the optical properties of the soft fibre. After the glass rod was removed, the now-hollow fibre could be mechanically deformed. Stretching along the axis of the fibre was accompanied by compression in the radial direction according to Poisson's ratio for elastic materials under strain. Therefore, the authors could tune the fibre colour from the starting colour to shorter wavelengths simply by stretching. Tuning the fibre colour to longer wavelengths could potentially be achieved by inducing swelling, and thereby increasing the thickness of the polymer layers, by exposure to organic solvents. This type of flexibility is not possible in the tropical fruit seed coat or in other natural structures made from hard materials.

Despite the potential of these soft photonic fibres, three main challenges remain: colour uniformity, colour purity and scalability. For the first problem, when the fibre is stretched along its axis, the strain is not uniformly

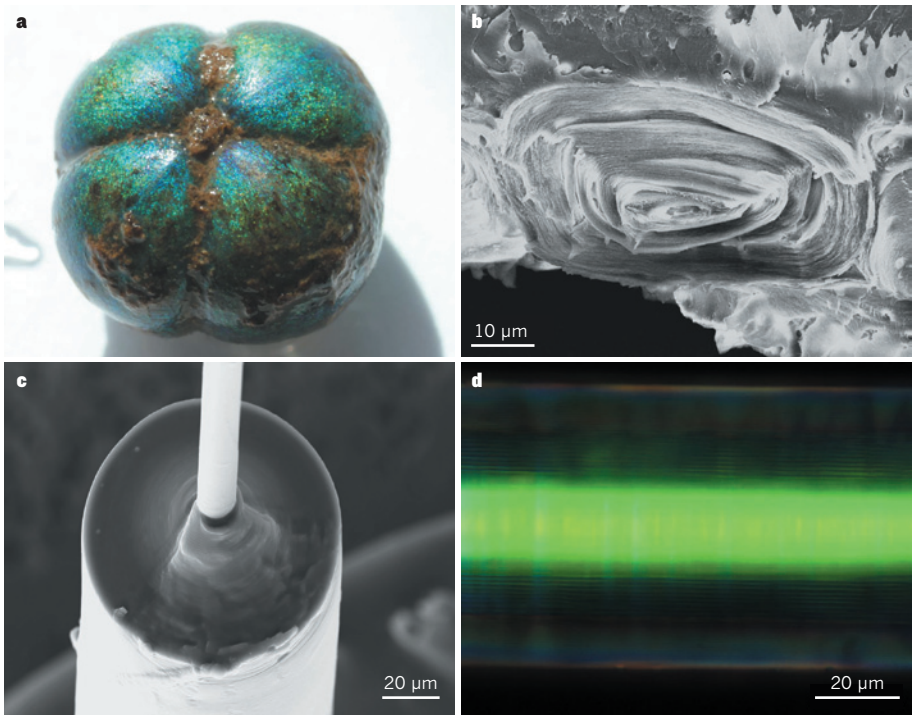

Figure 1 | Fruit-inspired optical fibres. **a**, The fruit of the tropical plant *Margaritaria nobilis* without its capsule (about 10 mm in diameter). **b**, Cross-section of the fruit seed coat shows a concentric, multilayered cellular structure. **c**, Cross-section of a soft multilayered optical fibre around a glass core, fabricated by Kolle and colleagues[3]. **d**, Reflected green colour from the soft optical fibre in **c**.