chains and the impacts of imported goods.

Such global assessments are a first step towards improving the sustainability of worldwide food production, because they provide fresh data and perspectives on the big picture and on the drivers of water use and abuse. A consideration of trade-related environmental concerns might also suggest new global water-governance solutions, which could be applied by introducing measures to ensure that existing food-trade frameworks of the European Single Market and the World Trade Organization are effective, sustainable and equitable. ■

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CANCER THERAPY

The leukaemia epigenome targeted

Modification of methyl groups attached to DNA alters gene expression, and mutations that deregulate this methylation are common in some leukaemias. Drugs that target aberrant methylation are emerging as promising therapeutics.

JULIE-AURORE LOSMAN

Only 20–40% of adults who have acute myeloid leukaemia (AML) survive in the long term[1]. Several large-scale genome-sequencing efforts have attempted to define mutations associated with AML, with a view to identifying new therapeutic strategies[2]. These analyses have uncovered many recurrent mutations in epigenetic regulator proteins, which modulate gene expression by altering the 3D structure of chromosomes. Epigenetic regulators include enzymes that attach and remove molecular modifications on DNA. Writing in *Cancer Discovery*, Yen *et al.*[3] and Shih *et al.*[4] present evidence that mutations in two enzymes, IDH2 and TET2, that lead to altered epigenetic regulation, can be targeted therapeutically in AML cells, providing a compelling rationale for further development of epigenetically targeted anticancer treatments.

The enzyme TET2 is a dioxygenase that depends on the molecule α-ketoglutarate (α-KG) for its activity (Fig. 1). It catalyses the addition of a hydroxyl group to 5-methylcytosine (5mC) — a form of the DNA base cytosine that has been modified by the attachment of a methyl moiety — to produce 5-hydroxymethylcytosine (5hmC)[5]. The formation of 5hmC is an important step in converting 5mC into unmethylated cytosine. Inactivating mutations in the *TET2* gene decrease 5hmC levels and lead to the accumulation of 5mC. This DNA hypermethylation leads to changes in gene expression that promote the proliferation of long-lived *TET2*-mutant haematopoietic stem cells, and disrupt their differentiation into various types of blood cell, thereby promoting AML.

Most other AML-associated mutations in genes that encode epigenetic regulators cause protein inactivation, but mutations in *IDH* genes are an exception. Both IDH1 and IDH2 are metabolic enzymes that normally catalyse the interconversion of α-KG and another molecule, isocitrate. But cancer-associated mutations alter their activity[6] such that they instead convert α-KG to (*R*)-2-hydroxyglutarate (2HG), which is structurally similar to α-KG and can competitively inhibit several α-KG-dependent enzymes[7], including TET2 (Fig. 1).

A previous study[8] showed that the leukaemic effects of mutant IDH enzymes require the sustained production of 2HG. Furthermore, drugs that inhibit the activity of mutant IDHs lower intracellular levels of 2HG and promote the differentiation of immature, *IDH*-mutant AML cells into mature white blood cells, both *in vitro* and in mice[9]. Mature white blood cells have a limited capacity to proliferate and are short-lived, so the inhibition of mutant IDH reduces the leukaemia-cell pool. However, these experiments were performed using 'tool' compounds, which, although highly potent, have not been pharmacologically optimized for use in humans.

In one of the two current studies, Yen *et al.*[3] developed a drug called AG-221, which is the first clinical-grade inhibitor that potently and selectively inhibits mutant IDH2. Treating patient-derived AML cells that harboured *IDH2* mutations with AG-221 reduced their levels of 2HG and induced them to

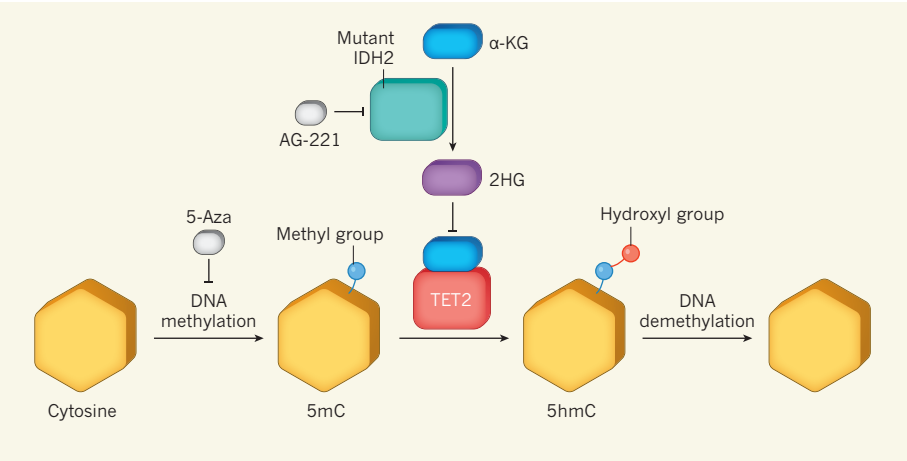

Figure 1 | The yin and yang of mutant IDH and TET2 proteins. Covalent linking of a methyl group to the DNA base cytosine by DNA-methylation enzymes produces 5-methylcytosine (5mC). The enzyme TET2, with the co-factor molecule α-ketoglutarate (α-KG), converts 5mC to 5-hydroxymethylcytosine (5hmC), which can be demethylated to form cytosine again. Mutations that cause the loss of TET2 function lead to accumulation of 5mc (not shown), which promotes acute myeloid leukaemia (AML). Mutant forms of IDH enzymes also promote AML. The enzymes convert α-KG to the structurally similar (*R*)-2-hydroxyglutarate (2HG), which competes with α-KG and so inhibits the activity of TET2. Yen *et al.*[3] developed a drug called AG-221 that inhibits mutant IDH2. The drug reduces 2HG levels and restores TET2 activity, thereby reversing 5mC accumulation in mouse models of *IDH*-mutant AML. Shih *et al.*[4] showed that a drug called 5-Aza has a similar effect in *Tet2*-mutant AML in mice. 5-Aza inhibits the conversion of cytosine to 5mC, thereby preventing 5mC from accumulating.

differentiate into mature white blood cells. Furthermore, treatment with AG-221 prolonged the survival of mice transplanted with the AML cells.

It remains to be seen whether these effects will be recapitulated in humans. However, preliminary results[10] from early-phase clinical trials of AG-221 suggest that the drug provides a therapeutic benefit in some people with *IDH2*-mutant AML. It is less clear whether it will have a similar effect on people who have solid tumours that harbour *IDH* mutations. In an ongoing phase I clinical trial to test a drug called AG-120 that inhibits mutant IDH1, interim analysis shows that the drug frequently stabilizes the disease in patients with solid tumours, but rarely causes tumour regression (see go.nature.com/2ngnxji).

Mutant IDH proteins are inherently tractable as therapeutic targets because their abnormal function can be inhibited. But restoring the activity of an inactivated enzyme such as TET2 is more difficult. The effect of TET2 loss is to increase DNA methylation, and there is evidence that some *TET2*-mutant blood cancers are hypersensitive to drugs that inhibit DNA methylation[11]. However, it is not clear whether this reflects a true therapeutic vulnerability of cells that lack TET2, or whether some other feature of these cancers is responsible for this sensitivity.

In the second study, Shih *et al.*[4] compared the effects of preventing DNA hypermethylation induced by genetic loss of *TET2* and restoring TET2 activity by inhibiting mutant IDH2 in AML. The authors generated mice that harboured mutations in either *Idh2* or *Tet2*, in combination with mutations in another gene, *Flt3*, which encodes a receptor tyrosine kinase protein (an enzyme that activates signalling pathways that promote the proliferation of blood-cell progenitors). Activating mutations in *FLT3* are common in AML. In mice, a *Flt3* mutation combined with either a *Tet2* mutation or an *Idh* mutation leads to AML.

The authors transplanted the leukaemic cells from their mutant mice into wild-type recipient animals to model conditions in patients, in whom both normal and leukaemic blood cells circulate. They then treated the recipient mice with either AG-221 or a drug called 5-azacytidine (5-Aza), which inhibits DNA methylation. Treatment of mice harbouring *Tet2*- and *Flt3*-mutant AML cells with 5-Aza decreased the level of DNA methylation and induced differentiation of the leukaemic cells — as did AG-221 treatment of mice harbouring *Idh2*- and *Flt3*-mutant AML cells. However, neither treatment significantly reduced the percentage of circulating blood cells that were derived from the donor mice, suggesting that neither killed a significant portion of the mutant cells.

Shih and colleagues next treated their *Tet2*- and *Flt3*-mutant mice with the FLT3 inhibitor AC-220 and 5-Aza, either alone or in combination, and treated their *Idh2*- and *Flt3*-mutant mice with AC-220 and AG-221, again either alone or together. Both combination treatments resulted in more-profound responses and increased the reversal of DNA hypermethylation more effectively than the single treatments. Tellingly, the combination therapies dramatically reduced the percentage of circulating cells that were derived from the donor mice, suggesting that two-pronged therapies that target both epigenetic dysregulation and kinase signalling can induce potent antileukaemic responses.

Together, the two current studies provide a valuable proof-of-concept that targeting epigenetic dysregulation could be an effective therapeutic strategy in AML. However, they also suggest that such approaches will not be sufficient to eradicate disease. Instead, Shih and colleagues' data indicate that the key to a cure might lie in dual-pronged therapies. Their work provides a compelling rationale for clinical trials of combined epigenetic- and kinase-targeted therapies.

Finally, it was unexpected that these combination therapies would kill AML cells, and this raises an interesting question: how do epigenetic dysregulation and proliferation-promoting signals interact in AML? Further studies will be required to rule out the possibility that inhibition of FLT3 signalling simply potentiates the effects of AG-221 and 5-Aza. However, if that is not what happens, then these findings suggest that there is a greater interplay between these (seemingly) functionally distinct pathways than is currently appreciated. A more thorough mechanistic understanding of how these pathways cooperate to promote leukaemia has the potential to uncover exciting new strategies to treat AML. ■

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PLANETARY SCIENCE

Reckless orbiting in the Solar System

Planets and most asteroids revolve around the Sun in the same direction. But an asteroid that shares Jupiter's orbit has been revolving in the opposite direction for about a million years. SEE LETTER P.687

HELENA MORAIS & FATHI NAMOUNI

The Solar System formed in a disk of gas and dust whose constituents revolved around the Sun in the same direction. In the final stages of planetary formation, trillions of bodies were expelled beyond the reach of the planets, forming a relatively thin disk of debris. The Galaxy's tidal forces then modified this structure into a spherical shell known as the Oort cloud that remains gravitationally bound to the Sun. This shell is located more than 10,000 times farther from the Sun than Jupiter is, and shelters objects that orbit the Sun in the direction opposite (retrograde) to that of planetary motion. On page 687, Wiegert *et al.*[1] report the discovery of the first object that shares the orbit of a planet but revolves in the retrograde direction.

Thousands of objects called Trojan asteroids populate Jupiter's orbit, revolving around the Sun in the same direction as the planet (prograde). These objects sit near Lagrange points, which form an equilateral triangle with the Sun and Jupiter. Whereas Trojan asteroids have stable orbits, other prograde asteroids can enter a transient co-orbital state for several thousand years[2], in which they have the same orbital period as a planet. Co-orbital states can take many shapes, depending on the asteroid's motion in space. These shapes include tadpoles, horseshoes, quasi-satellites — in which the asteroid stays close to the planet for many orbital periods — and combinations thereof (Fig. 1a).

The dynamics of most small bodies in the