TUMOUR BIOLOGY

Cancer-cell death ironed out

Ferroptosis is a form of cell death. The finding that cells that have certain mutations in the Hippo signalling pathway are susceptible to ferroptosis might offer a way to treat a cancer called mesothelioma. SEE LETTER P.402

DEAN FENNELL

In the late twentieth century, there was a rise in a type of cancer called mesothelioma, which is caused by exposure to asbestos used in building materials. Mesothelioma often arises decades after exposure, accounting for tens of thousands of deaths annually worldwide[1]. Even with the treatments currently available, it is inevitably fatal. There is therefore an urgent need to develop more effective therapies for this type of cancer. Wu *et al.*[2] report on page 402 that mutations in a cell-signalling pathway that commonly occur in mesothelioma create a tumour vulnerability that might be targeted to treat this disease.

Mesothelioma most often originates in the lining of the lungs, in cells that form the pleural membrane. Mutations frequently found in mesothelioma cells often inactivate proteins, called tumour suppressors, that function in anticancer pathways. One of the most common such inactivated proteins is called merlin (encoded by the *NF2* gene), which functions in the highly evolutionarily conserved Hippo signalling pathway. This pathway was originally identified in the fruit fly *Drosophila melanogaster*[3,4], and it comprises a signalling cascade that controls cell proliferation and organ size. If merlin or another protein in this pathway, such as LATS2, is inactivated, downstream proteins called YAP and TAZ can boost the expression of genes that promote tumour formation. Certain cancers can even become 'addicted' to YAP-mediated transcription for their survival[5].

However, if merlin, LATS2 and another protein called LATS1 are functional, YAP and TAZ undergo phosphorylation (a phosphate group is attached to them), which modifies the proteins and blocks their function by preventing them from entering the nucleus to drive gene expression[6]. Mutations in the genes encoding merlin and LATS2 are positively selected during tumour development[7], consistent with their normal roles as tumour-suppressor proteins in mesothelioma.

Wu and colleagues studied the gene-expression profiles of human cancer cells grown *in vitro*, and report that YAP and TAZ drive the expression of proteins, such as ACSL4, that are needed for a type of cell death called ferroptosis. The authors also uncovered a connection between the ability of cells to suppress ferroptosis and the cell–cell contact that depends on the protein E-cadherin. The authors report that high expression of E-cadherin in human mesothelioma cells grown *in vitro* is associated with resistance to ferroptosis. E-cadherin activates the Hippo pathway, and the authors went on to explore the relationship between this pathway and ferroptosis.

Cell death that occurs through ferroptosis depends on a reaction between cellular iron and hydrogen peroxide[8]. During ferroptosis, a polyunsaturated fatty acid — a type of lipid found in the cell membrane — undergoes a modification called peroxidation, which causes an increase in the level of molecules termed reactive oxygen species. Ferroptosis is often linked to depletion of the amino acid cysteine, which is imported into cells by the protein SLC7A11. Cysteine provides a building block for the production of glutathione, a molecule involved in a pathway that can combat ferroptosis.

The drug sorafenib is approved for clinical use. It can induce ferroptosis by inhibiting SLC7A11. The authors demonstrate that sorafenib treatment of cultured human mesothelioma cells that have mutations in the gene encoding merlin causes the cells to undergo ferroptosis. They report that this sensitivity to ferroptosis depends on YAP- and TAZ-mediated gene expression (Fig. 1).

Two independent clinical trials[9,10] found that sorafenib caused tumour shrinkage or stabilization in people with mesothelioma. However, neither trial evaluated the mutations present in the patients' tumours, and it is tempting to speculate that the tumours of people who responded particularly well had mutations that inhibited the Hippo signalling pathway and that thereby boosted

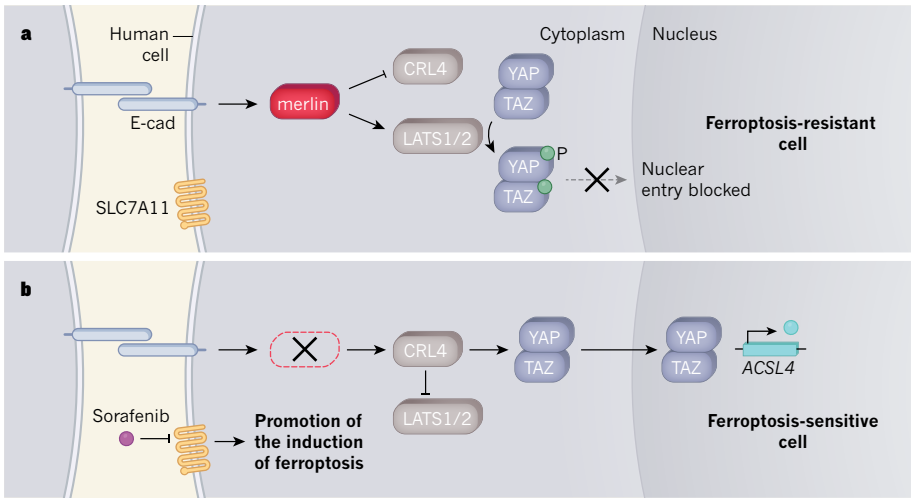

Figure 1 | Regulation of ferroptosis in human cells. Ferroptosis is a type of cell death whose induction is affected by a pathway that depends on the protein SLC7A11. Wu *et al.*[2] investigated how an anticancer signalling pathway called the Hippo pathway, in which mutations commonly occur in cancer cells, affects ferroptosis. **a**, Interactions between receptor proteins called E-cadherin (E-cad) on adjacent cells can trigger the Hippo pathway. A protein called merlin in this pathway prevents cancer-promoting gene expression by inhibiting a protein called CRL4. CRL4 inhibition enables the proteins LATS1 and LATS2 to add a phosphate group (P) to the proteins YAP and TAZ, and this phosphorylation prevents the proteins from entering the nucleus and driving gene expression. The authors report that YAP and TAZ drive the expression of genes that promote ferroptosis, revealing that Hippo pathway signalling makes cells resistant to ferroptosis. **b**, If merlin is not expressed because of a mutation, CRL4 is not inhibited and LATS1 and LATS2 cannot function. YAP and TAZ can enter the nucleus and drive the expression of genes, such as *ACSL4*, that promote ferroptosis. The authors report that tumour cells that lack merlin can undergo ferroptosis if treated with an inhibitor of SLC7A11, called sorafenib.

YAP- and TAZ-mediated gene expression.

Might other mutations beyond those in the Hippo pathway also regulate ferroptosis in mesothelioma? The most commonly mutated gene in this cancer[11] encodes the tumour-suppressor protein BAP1. This enzyme affects gene expression, and can cause a reduction in the expression of SLC7A11, which, in turn, leads to ferroptosis[12]. If the gene that encodes BAP1 is mutated, ferroptosis does not occur[12]. Therefore, the presence of wild-type BAP1 might help to enhance ferroptosis, along with any boost to ferroptosis provided by the use of SLC7A11 inhibitors. It is not known whether drugs that induce ferroptosis, such as sorafenib, would be effective in cells in which mutations inactivate BAP1.

Other approaches to targeting mesothelioma in which the Hippo pathway is inactivated are being explored. For example, in animal studies, loss of merlin expression is associated with cancer-cell vulnerability to inhibition of a protein called focal adhesion kinase[13]. However, no clinical benefit was found with this approach in a clinical trial[14]. Direct targeting of the interaction between YAP and TEAD, a protein to which YAP binds when it drives gene expression, is another strategy being pursued to block cancer-promoting gene expression[15]. Finally, YAP and TAZ recruit the protein BRD4 to drive the expression of specific genes, and use of a small-molecule inhibitor to target BRD4 can disrupt YAP- and TAZ-mediated gene expression[16]. This class of small-molecule inhibitor is entering early clinical trials. All of these approaches aim to block YAP- and TAZ-mediated gene expression. However, if the anticancer strategy being used aimed to trigger ferroptosis in mesothelioma cells, then YAP- and TAZ-mediated gene expression would be required.

Identifying a tumour that has an inactivated Hippo signalling pathway as a means of a developing personalized cancer therapy — the ultimate goal — poses some challenges for mesothelioma. Focusing only on tumours that have lost merlin function would probably miss mesotheliomas in which Hippo signalling is inhibited by inactivation of other proteins, such as LATS1 and LATS2. A previous study[17] of the Hippo pathway in various cancers has revealed that 22 genes are commonly transcribed by YAP and TAZ, and this transcriptional profile might offer a way to identify ferroptosis-sensitive tumours. Furthermore, because this profile was found[17] in several types of tumour, triggering ferroptosis might be worth exploring for cancers other than mesothelioma.

Wu and colleagues' report highlights a strategy that could offer a way of developing a personally tailored anticancer therapy. However, therapies targeted to mutations in an individual's mesothelioma are still in their infancy. Clinical trials that take this approach, for example the mesothelioma stratified therapy trial in which I am involved (see go.nature.com/2o19lah), might help to make progress in such endeavours, and provide improved treatments at a time of unmet clinical need. ■

Dean Fennell *is at the Mesothelioma Research Programme, Leicester Cancer Research Centre, University of Leicester, and at the University Hospitals of Leicester NHS Trust, Leicester LE2 7LX, UK.*
e-mail: df132@leicester.ac.uk

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PLANETARY SCIENCE

Signs that Jupiter was mixed by a giant impact

Simulations suggest that Jupiter's dilute core might be the result of a collision between the planet and a Uranus-mass planetary embryo. This finding indicates that giant impacts could be common during planet formation. SEE LETTER P.355

TRISTAN GUILLOT

In the past couple of years, NASA's Juno spacecraft has measured Jupiter's gravitational field with exquisite accuracy[1,2]. The results have revealed that the planet's fluid hydrogen–helium envelope does not have a uniform composition: the inner part contains more heavy elements than the outer part[3,4]. On page 355, Liu *et al.*[5] propose that this asymmetry resulted from a head-on collision between the young Jupiter and a planetary embryo that had a mass about ten times that of Earth. The authors suggest that the primordial cores of the planet and of the embryo would have merged and then partially mixed with Jupiter's envelope, explaining the structure of the planet seen today.

Scars of impacts abound on rocky planetary bodies. For example, the Moon is covered in craters, and was formed by a collision that occurred 4.5 billion years ago between Earth and a massive body[6]. Although impacts leave no direct imprint on the surfaces of fluid planets, the tilts of the rotational axes of Saturn (27°), Uranus (98°) and Neptune (30°) might indicate that violent collisions occurred in the past[7]. After all, it is known that massive planetary embryos on the order of ten Earth masses must have been present in the early Solar System[8], in addition to the planets that are still here. Jupiter, with its small tilt (3°), seems to have escaped unscathed[7]. But according to Liu and colleagues, this was not the case.

Jupiter is mostly made of hydrogen and helium. However, observations of its atmospheric composition[9] and gravitational field show that it contains a non-negligible proportion of heavier elements in the form of a central core and in the hydrogen–helium envelope. This envelope is fluid and is expected to be largely convective[10], so it was surprising when Juno revealed that the envelope's composition is not uniform. Instead, the core seems to be partially diluted in the envelope, extending to almost half of the planet's radius[3,4] (Fig. 1).

Producing this internal structure directly would require the delivery (accretion) of 10–20 Earth masses[3,4] of heavy elements to the young Jupiter after the core had formed and during the first half of the growth of the envelope. The accretion of this material would need to have stopped after the planet had grown to about half of its present mass.

Formation models indicate that this hypothesis is unlikely. In these models, when Jupiter reaches about 30 Earth masses, the growth of the envelope by accretion is fast[11], and the planet efficiently pushes away any dust particle that is millimetre-sized or larger[12]. As a result, the envelope should be poor in heavy elements. Any subsequent delivery of heavy elements by planetesimals (the asteroid-sized precursors of planets) or small planets is inefficient and cannot explain a heavy-element abundance that would increase with depth, as is observed. Erosion of the core into the envelope is possible[10,13], but simulations show that this process tends to remove any small composition gradients that exist in the