

# News & views

## Cancer

# Powerful system for cell protection revealed

Brent R. Stockwell

The discovery of a mechanism that guards against a type of cell death called ferroptosis reveals a system that regenerates a ubiquitous protective component of biological membranes, and might offer a target for anticancer drugs.

On 3 December 1956, the biochemist Frederick Crane detected, for the first time ever, a yellow substance purified from cow hearts, which had been obtained from the Oscar Mayer meat-processing factory in Madison, Wisconsin<sup>1</sup>. In the laboratory of David Green at the University of Wisconsin, Crane investigated the oily material he had discovered, and struck gold: he found a lipid molecule that has a crucial role in energy generation in cells. But there were hints that it might have another function. Now, writing in *Nature*, Doll *et al.*<sup>2</sup> and Bersuker *et al.*<sup>3</sup> report the discovery of this elusive role, finally revealing the missing part of the puzzle 63 years after Crane's discovery.

When Crane analysed the molecule he had identified, he noted that it was structurally similar to certain vitamins, and it was initially named vitamin Q<sub>10</sub>. This molecule is important for respiration<sup>1</sup> – the energy-generating process that makes the molecule ATP – and acts in mitochondria, organelles that are responsible for much of the energy production in cells. It was subsequently discovered<sup>1</sup> to be ubiquitous. It not only resides in mitochondria, but is also present elsewhere in the cell in almost all lipid membranes.

The molecule was renamed ubiquinone because of its ubiquity and because it contains a type of chemical structure known as a quinone. Ubiquinone now also goes by the name coenzyme Q<sub>10</sub>. But its function outside mitochondria has remained enigmatic, until now.

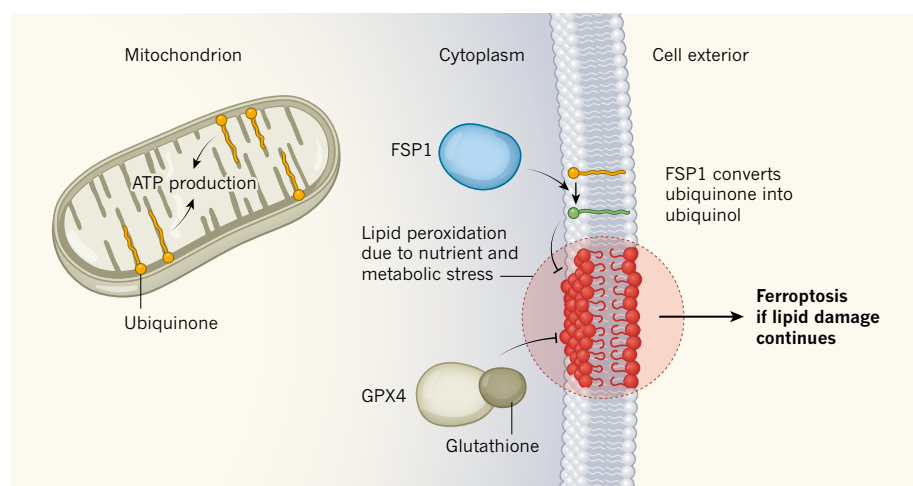
In 2012, a previously unknown type of programmed cell death called ferroptosis was described<sup>4</sup>. This iron-dependent pathway causes cells to die when a lipid modification called peroxidation degrades their membranes (Fig. 1). Ferroptosis has been linked to a range of processes. For example, it has been implicated

in degenerative diseases; in damage to plants caused by climate-change-associated heat stress; and in natural functions of the immune system, such as the elimination of tumour cells by killer T cells<sup>5–7</sup>. Therapeutic approaches that harness ferroptosis are being developed for some cancers, given that the abnormalities of certain tumour cells can make them vulnerable to this type of cell death.

The damage to cell membranes that occurs during ferroptosis can be prevented by a protein called GPX4 acting together with a small

peptide called glutathione<sup>8</sup>, which confers antioxidant properties by combating lipid damage caused by peroxidation. As a consequence, approaches that inhibit GPX4 and that deplete glutathione from cells have recently been examined as potential anticancer strategies<sup>9</sup>. In 2016, researchers developed FIN56, a chemical that can induce ferroptosis, and this tool provided a clue that there might be another mechanism, besides GPX4- and glutathione-mediated repair, that protects against this process<sup>10</sup>. FIN56 was found to kill cells by perturbing a metabolic pathway called the mevalonate pathway, which acts upstream of ubiquinone synthesis; furthermore, supplementing cells with idebenone, a synthetic compound that is similar to ubiquinone, prevented FIN56 lethality, suggesting that FIN56 functions by depleting ubiquinone<sup>10</sup>. This previous work raised the question of whether ubiquinone normally functions to protect cells from ferroptosis. However, because FIN56 can deplete both ubiquinone and GPX4, it was difficult to draw any definitive conclusions.

Doll *et al.* and Bersuker *et al.* hypothesized that cells have a way of protecting themselves against ferroptosis even in the absence of GPX4. This was a heretical idea given that, during the short history of ferroptosis research, the dogma that GPX4 is essential to guard



**Figure 1 | A pathway that blocks cell death.** Doll *et al.*<sup>2</sup> and Bersuker *et al.*<sup>3</sup> report studies revealing that the FSP1 protein protects human cells from a type of cell death called ferroptosis. Some tumour cells are susceptible to ferroptosis, and this insight about FSP1 is of clinical interest. The finding has also uncovered a previously unknown role for a lipid called ubiquinone. Ubiquinone is found in lipid membranes, including those of an organelle called a mitochondrion, where it aids production of the molecule ATP, the cell's energy carrier<sup>1</sup>. The authors report that FSP1 targets ubiquinone in the cell membrane to generate a reduced form of the molecule, called ubiquinol (green). Ferroptosis occurs if a form of lipid modification called peroxidation (red) damages the cell membrane; however, ubiquinol inhibits peroxidation and blocks ferroptosis. FSP1 acts independently of another pathway known to block lipid peroxidation and ferroptosis<sup>8</sup>, which requires the proteins GPX4 and glutathione.

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against ferroptosis in all contexts had already been established. Nevertheless, these two teams searched for other such protective mechanisms. Both groups analysed human cells grown *in vitro* to test whether any components block ferroptosis when GPX4 is not present, and they independently identified a gene encoding a protein that they name ferroptosis suppressor protein 1 (FSP1), which was previously called AIFM2.

Excitingly, the authors discovered that FSP1 replenishes a reduced form of ubiquinone, called ubiquinol, that acts protectively by combating the lipid peroxidation that drives ferroptosis. Further experiments revealed that this FSP1-dependent modification of ubiquinone, in locations other than mitochondria, acts to protect against ferroptosis. The comic-book superhero Green Lantern has a power

ring that needs to be recharged once its protective energy becomes depleted, and, by analogy, FSP1's role in generating protective ubiquinol could be a similarly crucial recharging process.

The identification of this FSP1-mediated process suggests that drugs that inhibit FSP1 might be developed as anticancer treatments. Doll *et al.* and Bersuker *et al.* found that the level of resistance to ferroptosis across many human cancer cell lines grown *in vitro* correlates with the amount of FSP1 present in the cells, suggesting that modulating FSP1 might have clinical relevance. It would also be worth investigating whether treatments that boost FSP1 activity are useful as therapies for degenerative diseases driven by ferroptosis. These two latest studies clearly suggest that the mysteries of ferroptosis continue to yield important biological and therapeutic insights.

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The author declares competing financial interests: see [go.nature.com/2bdv9eq](https://www.nature.com/2bdv9eq) for details.