nanocubes will absorb or emit light in processes associated with electronic transitions), leads to an unusual radiation phenomenon known as superfluorescence. In this effect, laser excitation of the nanocubes causes a spontaneous macroscopic optical polarization that results in an intense burst of light from the nanocubes.

Superfluorescence has previously been observed in superlattices formed from $CsPbBr_3$ nanocubes alone[8]. However, the flexibility with which the periodicity, packing density and orientation of the highly fluorescent $CsPbBr_3$ nanocubes in Cherniukh and colleagues' superlattices can be tailored opens up fresh avenues of research into this phenomenon. The superfluorescence pulses were as short as 22 picoseconds (1 ps is 10^{-12} seconds), which makes these superlattices attractive potential candidates for use as highly energy-efficient, ultrafast light emitters.

What is next for this field of research? It seems feasible that the family of superlattices will expand still further: Cherniukh *et al.* briefly report that they have also made binary superlattices that have a columnar structure, and others that have an arrangement analogous to the crystal structure of aluminium diboride (which consists of sheets of boron atoms interleaved by layers of aluminium atoms).

The findings could also aid the development of applications for superfluorescence – which has been observed in a wide variety of atomic, molecular and nanoscale systems[9], but has not yet been used in a device. The ability to customize the 3D structures of superlattices might provide a way to tailor superfluorescence at will, and thereby enable its use, for example, as a quantum light source. This, in turn, might require further efforts to improve the 3D ordering of superlattices, and to increase the size of the materials that can be made in which the ordering is strictly maintained. Research might also be needed to stabilize the ordered structure when superlattices are incorporated into a device, probably by using linker molecules between the nanocrystals.

In the meantime, the new findings open the way for researchers to try out many combinations of nanocrystals that have various attributes – such as emissive, magnetic or insulating properties – as building blocks for superlattices. This could result in materials with multiple functionalities, all of which could be controlled by the spatial arrangement and distance between the nanocrystals.

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Cancer

Mitochondrial gatekeeper of cell death by ferroptosis

Javier Garcia-Bermudez & Kıvanç Birsoy

Ferroptosis is a type of cell death driven by oxidative damage to lipid membranes. The discovery that organelles called mitochondria have an antioxidant system that counteracts ferroptosis might lead to new anticancer therapies. **See p.586**

Mitochondria, the organelles that enable our cells to generate energy, are thought to have evolved from formerly free-living, oxygen-dependent microorganisms[1]. However, oxygen-dependent energy production using an organelle enclosed by lipid membranes comes at a cost. Such respiration often generates reactive oxygen species (ROS), which can damage cellular structures and compromise their function. For example, ROS react with membrane lipids in a process termed lipid peroxidation, and the resulting abnormal lipid peroxides ultimately trigger an iron-dependent form of regulated cell death called ferroptosis[2]. Cells use multiple protection and repair systems to combat the toxic effects of these modified membrane lipids. On page 586, Mao *et al.*[3] report the discovery of a system that protects mitochondrial lipids from oxidative damage.

Mammalian cells rely on three main systems to repair lipid peroxides. The key proteins that underpin the three systems are, respectively, GPX4, FSP1 and DHFR[2,4–6]. Each of these antioxidant repair nodes also involves a metabolite molecule that exists in chemically reduced and oxidized states. Among these, ubiquinone (also known as coenzyme Q_{10}) is a lipid that has functions in both mitochondrial membranes and the cell membrane. The reduced form of ubiquinone, termed ubiquinol, has antioxidant properties and can repair lipid peroxides.

Cells need to continuously replenish ubiquinol to retain this protective function for their membrane lipids. The enzyme FSP1 counteracts ferroptosis by generating ubiquinol from ubiquinone, but FSP1 activity is restricted to the cell membrane[4,5]. This finding raised the question of whether

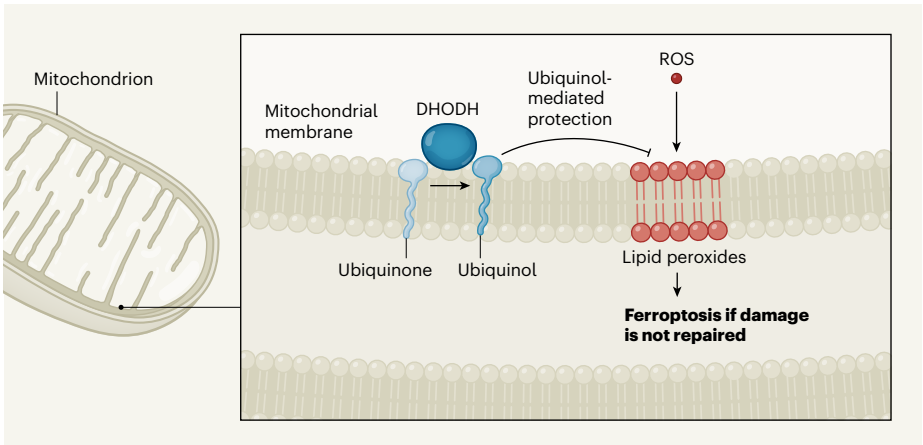

Figure 1 | A system for repairing mitochondrial lipids. Energy-generating processes in mitochondria produce reactive oxygen species (ROS), which can damage the organelle's membrane lipids through oxidation. This process forms toxic lipids, termed lipid peroxides, which can trigger a type of cell death called ferroptosis. Mao *et al.*[3] report the identification of a system that protects mitochondrial organelles. The enzyme DHODH converts the molecule ubiquinone to ubiquinol, which helps to combat the effects of lipid peroxidation and protects cells from ferroptosis.

mitochondria exploit a similar mechanism to generate ubiquinol and thereby repair oxidative damage to mitochondrial membrane lipids.

Mao and colleagues hypothesized that a system mitigating lipid peroxidation also exists in mitochondria. Given the close relationship between cellular metabolism and ferroptosis, the authors focused on metabolite molecules that are altered in cancer cells on lipid peroxidation. Surprisingly, they observed that peroxidation is associated with substantial changes in the abundance of metabolites in the pathway that synthesizes the pyrimidine bases that are a component of DNA and RNA. Building on this observation, the authors investigated the possibility that a component of this synthesis pathway is involved in preventing ferroptosis.

Most of the components of this pathway exist in the cytoplasm, but one enzyme, DHODH, is found in mitochondria. DHODH catalyses the conversion of the molecule dihydroorotate to orotate through an oxidation reaction that uses ubiquinone and thereby generates ubiquinol. Further experiments by Mao *et al.* revealed that DHODH protects cells against lipid peroxidation by regenerating ubiquinol, enabling ubiquinol-mediated repair of oxidative damage to mitochondrial lipids (Fig. 1). Supplementing cells with the end products of the pyrimidine-synthesis pathway did not affect lipid peroxidation, demonstrating that this anti-ferroptotic role of DHODH is independent of its function in pyrimidine synthesis.

These findings establish DHODH-mediated regulation of ubiquinol production as an efficient system for the mitigation of lipid peroxidation exclusively in mitochondria, in a mechanism that has echoes of the FSP1 system. Interestingly, a version of the GPX4 protein is found in the mitochondria of some cells, and its level of expression varies in different types of cancer. This mitochondrially localized GPX4 is not essential for mouse survival[7], indicating that it has a redundant role. By contrast, DHODH is ubiquitously expressed and has a role in cell proliferation owing to its function in nucleotide synthesis. Rapidly dividing cells, such as cancer cells, might therefore take advantage of this active pathway as a way to inhibit lipid peroxidation.

Indeed, Mao and colleagues found that if human tumour cells that expressed low levels of GPX4 were transplanted into mice treated with an inhibitor of DHODH, the resulting loss of DHODH function led to ferroptosis of the cells and impaired tumour growth. The effect was independent of DHODH's role in pyrimidine synthesis. It remains to be seen whether this mitochondrial ferroptosis-blocking antioxidant system contributes to the spread of cancer cells through metastasis[8] or to the tumour response to radiotherapy[9]. These are processes in which the induction of ferroptosis might help to thwart tumour progression. Potent DHODH inhibitors are being developed as anticancer agents, and are currently undergoing clinical trials. Perhaps they will be particularly effective in cancer cells that have low levels of expression of GPX4.

Mao and colleagues' discovery of a system for the specific protection of mitochondrial membranes suggests that dedicated mechanisms to counteract lipid peroxidation might exist in other subcellular compartments. Interestingly, squalene, which is an intermediate molecule in the biosynthetic pathway that generates cholesterol, protects cancers called lymphomas from lipid peroxidation, and is found in high concentrations in lipid droplets[10]. However, it is unclear whether squalene's protective function is due to this specific localization to droplets.

"Potent inhibitors of this enzyme are being developed as anticancer agents."

Organelles such as the endoplasmic reticulum and peroxisomes also harbour ROS-generating reactions. Glutathione and tetrahydrobiopterin are redox-active molecules (which can alter the oxidation state of other molecules), and thus might offer alternative ways to combat lipid peroxidation in such cases. However, the precise mechanisms and components that could enable the transport of these molecules to organelles are poorly understood. Advances in ways of assessing the molecular and protein compositions of organelles, through techniques such as metabolomics and proteomics, should provide insights into this fundamental issue, and improve our understanding of the role of antioxidants in tumour progression.

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Complexity science

Law of human travel uncovered

Laura Alessandretti & Sune Lehmann

An analysis of mobile-phone tracking data has revealed a universal pattern that describes the interplay between the distances travelled by humans on trips and the frequency with which those trips are made. **See p.522**

As a scientist, you sometimes come across a finding that is clear and robust, revealing a pattern that was right in front of you all along – and which makes you want to kick yourself for not noticing it before. The universal visitation law of human mobility, reported on page 522 by Schläpfer *et al.*[1], is just such a finding. The authors uncover a pattern of human behaviour that connects travel distance to the frequency of trips.

Consider any two places. Can we predict how many people travel from one to the other, and vice versa, on the basis of the position and simple characteristics of the two locations? This question is at the core of a large body of literature whose origin dates back to the mid-nineteenth century. In 1885, the geographer Ernst Ravenstein showed empirically that two key elements explain the number of individuals who move between any two places[2]: the distance between the places, and the socio-economic properties of the origin and destination. The number of travellers tends to decrease with distance, for example, and more-populated places attract more travellers.