particles' indistinguishability, which means that there is no measurable difference between the two outcomes in which the particles exit along different paths. The overall output phases of these indistinguishable outcomes are opposite to each other, and when added together using quantum rules for bosons (particles with integer spin, a quantum property common to both photons and helium-4 atoms), these two possible outcomes interfere and cancel. The only outcomes remaining are those with two particles in a single output. As a result, simultaneous single-particle detections ('coincidence counts') at both outputs are forbidden.

Lopes *et al.* demonstrate two-particle quantum interference with helium-4 atoms. In their experiments, the atoms' paths are related to their speeds, which are manipulated by selectively transferring momentum to and from light in absorption and emission processes[5,6]. First, the researchers prepared a 'twin pair' by removing from an atom reservoir indistinguishable atoms with different speeds. Second, they used light pulses to modify the atoms' momenta and cause the pair to meet; the atom in the first path travels with velocity v_1 and the atom in the second path with v_2. A beam-splitting mechanism implemented reflection and transmission by changing the atoms' speeds with 50% probability from v_1 to v_2 and vice versa.

The atoms continued to travel until they hit a time-resolved, multipixel atom-counting detector, at which an atom with v_1 would arrive at a different time from one with v_2. Lopes and colleagues prepared many twin pairs in a short interval and recorded the precise location and timing of the atoms' arrivals at the detector: a coincident count would be the measurement at a particular location of a particle at time t_1 followed by a measurement at t_2. Although the researchers found that the arrivals from the many pairs were distributed in two time windows (corresponding to the two output paths), they found a striking lack of instances among these random outcomes when the time difference was exactly $t_2 - t_1$, indicating that the atoms from a twin pair must be exiting the beam-splitter with the same velocity. This 'anticorrelation' is the signature of a HOM experiment.

As in quantum-optics demonstrations of the HOM effect, the present result demonstrates that pairs of identical, 'quantum-entangled' particles have been produced. The unique capabilities of this apparatus, including the combination of condensed metastable helium-4 atoms and the atom-counting detector, offer a spatial and temporal resolution unavailable to others. Protocols for transmitting and processing quantum information, analogous to those used in optical systems, can now be implemented with new capabilities in atomic systems: atoms, unlike photons, may interact with one another, and because they have mass, their mechanical properties, such as momentum, can be varied and used as experimental parameters.

Furthermore, because atoms can also be fermions (particles with half-integer spin, such as electrons), they could exhibit a quantum-interference effect that is the fermionic equivalent of the HOM effect[4]. Evidence for this mechanism has already been seen in electronic systems[7]. The bosonic HOM effect demonstrated here, and its fermionic counterpart, may offer new possibilities for implementing quantum-information protocols and for exploring the foundations of quantum physics. ■

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CANCER

A piece of the p53 puzzle

An iron-dependent form of cell death called ferroptosis has been implicated as a component of the tumour-suppressor activity of p53, providing fresh insight into how this protein prevents cancer development. SEE ARTICLE P.57

KATHRYN T. BIEGING & LAURA D. ATTARDI

The gene that encodes the p53 tumour-suppressor protein is the most commonly mutated gene in human cancers[1]. Indeed, p53 is inactivated in more than half of all cancers, reflecting the fact that it provides a crucial brake to cancer development, and that incapacitating p53 is often a requisite step for the emergence of cancer. However, despite years of research, our understanding of how p53 performs its job remains far from complete. In this issue, Jiang *et al.*[2] (page 57) uncover a previously unknown role for p53 in regulating a type of cell death dubbed ferroptosis, completing one more piece of the p53 puzzle.

Conventionally, p53 is thought of as a sentinel for DNA damage. In this role as a guardian of the genome, p53 responds to DNA damage either by putting the brakes on proliferation, allowing cells to pause and repair damaged DNA before dividing, or by driving a form of cell suicide called apoptosis, both of which protect against the accumulation of mutant cells that have the potential to

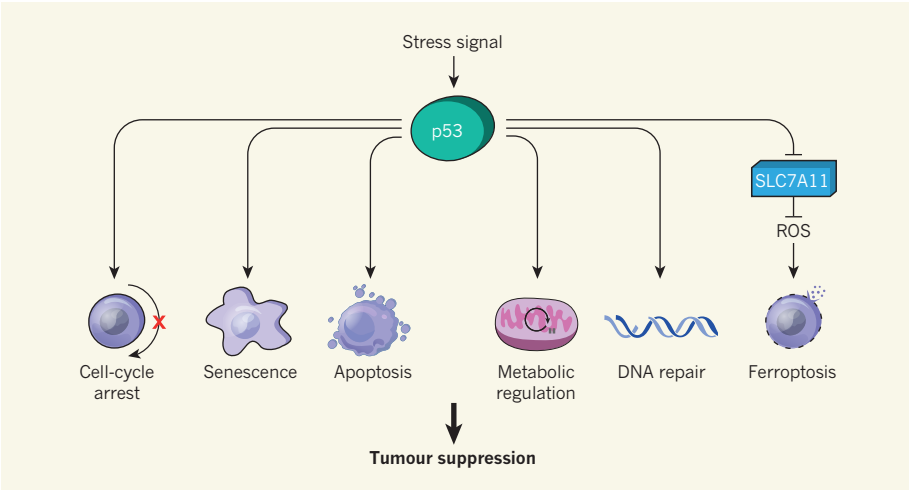

Figure 1 | The functions of p53 in tumour suppression. Activation of p53 in response to stress signals leads to diverse cellular responses. Conventionally, the tumour-suppressor activity of p53 has been attributed to its ability to induce cell-cycle arrest, senescence and a form of cell death called apoptosis in response to DNA damage or the expression of cancer-promoting genes. However, studies indicate that other p53-mediated activities, such as metabolic regulation or DNA repair, might be needed for tumour suppression, or might compensate when these classical functions are absent. Jiang *et al.*[2] show that p53 represses the target gene *SLC7A11* to promote the accumulation of reactive oxygen species (ROS), triggering a non-apoptotic form of cell death called ferroptosis that suppresses tumour growth.

fuel cancer development[3,4]. The protein fulfils this responsibility in large part by serving as a transcription factor that, among its many target genes, modulates the expression of genes encoding proteins that inhibit cell division or induce apoptosis[4].

Although this regulatory role as a guardian of the genome seems to account for p53's tumour-suppressor function, several studies have altered our thinking about how p53 represses cancer development. A set of papers (including one from the authors of the current study) provided pivotal evidence that p53-mediated apoptosis and proliferative arrest in response to DNA-damage signals are dispensable for tumour suppression[5–7]. These studies illuminated the functions of p53 that are not essential for tumour suppression, but failed to definitively reveal which p53 functions are required. Jiang and colleagues' latest study sheds light on this issue.

The authors use a mutated form of p53 called $p53^{3KR}$, which carries alterations at several key sites in its DNA-targeting region. As such, $p53^{3KR}$ has an impaired ability to activate many of p53's target genes, including those responsible for the protein's anti-proliferative and pro-apoptotic activity. The mutated protein nonetheless suppresses spontaneous tumour development in mice[6] — but how? The authors embark on an unbiased quest to answer this question by searching for potential mediators of p53 tumour-suppressor function. They identify *SLC7A11* as a gene whose expression is repressed by both p53 and $p53^{3KR}$.

SLC7A11 is a cell-surface, amino-acid transporter protein that dampens the production of reactive oxygen species (ROS), which can wreak havoc in a cell by inducing damage[8]. In particular, by limiting ROS accumulation, SLC7A11 inhibits ferroptosis, a form of non-apoptotic cell death triggered by the iron-dependent production of ROS[9] (Fig. 1). Jiang *et al.* show that both p53 and $p53^{3KR}$ can stimulate ferroptosis *in vitro* in response to the ferroptosis-activating agent erastin, and that this response can be inhibited by the overproduction of SLC7A11. This contrasts starkly with the inability of $p53^{3KR}$ to regulate classical p53 functions, and suggests that the ability to induce ferroptosis could account for the function of $p53^{3KR}$ in mice.

To test this hypothesis, the authors analyse mouse embryos carrying $p53^{3KR}$ but lacking the protein Mdm2, an essential inhibitor of p53. These mutant embryos normally die as a result of hyperactive p53 signalling, but the authors show that inhibiting ferroptosis imparts some protection against this lethality. These experiments provide evidence that ferroptosis contributes to p53 activity *in vivo*, in this case promoting embryonic lethality.

Expanding this analysis to cancer development, Jiang and colleagues next show that overexpression of SLC7A11 overcomes the tumour-suppressor effects of $p53^{3KR}$ in tumours transplanted into mice. This suggests that repression of SLC7A11 transcription is necessary for $p53^{3KR}$-mediated tumour suppression, and, moreover, that $p53^{3KR}$ suppresses tumour growth at least in part through ferroptosis. However, it remains unclear whether p53-mediated activation of ferroptosis is a front-line tumour-suppressive response or whether it primarily provides a back-up mechanism when other p53 functions are crippled, as in the $p53^{3KR}$ mutant.

This study unveils a new pathway for p53-dependent tumour suppression. However, many questions remain. For instance, it is still unknown whether ferroptosis is a general mechanism that operates in all tumour types or whether it has a more selective function, suppressing cancers that originate from specific tissues. It is also not yet clear which p53-activating signals — such as expression of cancer-promoting genes or deprivation of nutrients — activate ferroptosis *in vivo*. The roles of other p53 target genes in ferroptosis must also be defined.

In the broader landscape, it will be imperative to determine which other p53-dependent processes contribute to tumour suppression and what their context dependencies may be[10]. Although DNA-damage-induced apoptosis and cell-cycle arrest have been deemed to be dispensable for tumour suppression, this does not preclude a role for these responses in some settings. Finally, the finding that inducing ferroptosis by using an erastin analogue delays the growth of p53-expressing tumours in a mouse transplant model[11] suggests that activating ferroptosis may be a promising therapeutic strategy for treating tumours in which p53 activity is retained, a possibility that warrants further investigation. ■

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BIODIVERSITY

Land use matters

A meta-analysis at a local scale reveals that land-use change has caused species richness to decline by approximately 8.1% on average globally, mainly as a result of large increases in croplands and pastures. SEE ARTICLE P.45

BRIAN MCGILL

The main effects humans have on our planet seem to manifest in factors of two: we have doubled the rate at which nitrogen enters the biosphere by using fertilizer; we have diverted half of the fresh water and half of all plant productivity for our own purposes; and we have modified about half of the planet's land[1,2]. It is widely speculated that the last of these — modifying roughly 50% of all land — is the biggest human-caused threat to biodiversity, but this theory has never been comprehensively assessed. On page 45 of this issue, Newbold *et al.*[3] describe an ambitious attempt to evaluate the global impact of land-use change on terrestrial biodiversity.

The authors assembled a data set of more than 380 previous studies comparing the biodiversity of sites with no human change (original or primary vegetation) with similar sites modified for human use. They combined this data set with further data on the global land-use changes made by humans over the past 500 years[4], and also with several predictions of how humans might modify land use over the next 100 years. The processes controlling biodiversity are highly scale-specific[5], and most previous studies have focused either on extinctions at global scales or on the number of species in certain regions (and the latter is actually often increasing[6]). By contrast, Newbold *et al.* analysed their data at a local scale, typically smaller than a football field, which is more relevant to the way humans interact with nature.

The headline finding is that land-use change has caused the number of species (species richness) contained in these small plots of land to decline by 8.1% over 500 years when averaged across the globe. The authors also find a 10.7% decline in the number of individual organisms, with an additional decline in richness resulting from this loss of individuals rather