Laser-cooling methods were first reported[6,7] in 1975, and have since been widely developed to reduce the motion of particles. This approach works well for atoms, but not for particles that do not absorb light, such as protons. Scientists have therefore invented other cooling methods, such as resistive cooling[8] (in which ions dissipate their energy by inducing a current in a cold electric circuit) and synchrotron cooling[9] (in which fast-rotating particles with low mass radiate energy by emitting electromagnetic radiation). However, the lowest particle temperatures achieved using those approaches are roughly 1,000 to one million times higher than those of laser-cooled atoms.

An interesting alternative is to cool a charged particle by bringing it close to another, colder charged particle[10] — an approach commonly known as sympathetic cooling. For example, consider a positively charged atomic ion that is being continuously laser-cooled to one-thousandth of a kelvin, and which is then brought close to a proton that is initially at 4 K in an ion trap. The proton and ion will repel each other within the confinement of the ion trap, effectively transferring kinetic energy from the proton to the ion. Because the ion is constantly being laser-cooled, the repulsive interactions will eventually chill the proton to the same temperature as the ion, even though the proton is not being cooled directly.

Sympathetic cooling works well, but the nearby presence of an ion would be undesirable when making ultraprecise measurements of a proton's properties. Furthermore, the method requires that the particle and the ion have charges of the same polarity, to provide the necessary repulsive interactions. Bohman and colleagues' work provides a potential solution to these issues.

The authors used separate Penning traps to confine a cloud of beryllium ions and a proton in an ultrahigh vacuum, and continuously laser-cooled the ions (Fig. 1). The proton and the ions were then set up to 'talk' to an electrical resonator circuit, which enables the two trapped-particle systems to interact only when the natural oscillation frequencies (the resonance frequencies) of the two systems match exactly. Bohman *et al.* demonstrated the influence of the ions on the proton using an established technique, in which electrical 'noise' in the resonator circuit is analysed to directly determine the temperatures of the two systems.

To further ensure that the proton cooling is indeed caused by the ions, the authors fixed the oscillation frequency of the proton, and then varied the oscillation frequency of the ions. They observed that cooling interactions occurred only when the ions' natural oscillation frequency matched that of both the proton and the resonator circuit, as expected. Furthermore, the researchers found that numerical simulations of the cooling set-up matched the observed experimental result, confirming the ions' proton-cooling influence.

Impressively, Bohman *et al.* show that the proton temperature can be reduced by 85%, which would be a substantial amount in an ultraprecise measurement of a fundamental particle. The authors' technique opens up the possibility of being able to cool any charged particle by 'wiring it up' to laser-cooled ions, with any distance between the particle and the ions.

The results also have implications for research in quantum information. A goal for this field is to exchange single bits of quantum information between spatially separated quantum systems. However, it is challenging to do this using a conducting wire. Bohman and colleagues' findings suggest a possible solution to this problem, but it will first be necessary to broaden our understanding of how single quanta of energy are exchanged over large distances, and to greatly improve the rate of energy exchange between the separated systems.

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Cancer

A persistent look at how tumours evade therapy

Karen Gomez & Raul Rabadan

Understanding how resistance to chemotherapy occurs could lead to better anticancer treatments. Persister cells in tumours can contribute to this resistance. A method to characterize these cells in detail sheds light on their origins. **See p.576**

Cancer can recur when a subset of tumour cells, called persister cells, survive chemotherapy. Most of these persisters are non-dividing (quiescent) in the presence of the therapeutic drug, but a rare subpopulation can re-enter the cell cycle during treatment, which enables them to proliferate. Much research has focused on the genetic mechanisms underlying such resistance to treatment. However, emerging data suggest that non-genetic mechanisms (such as changes to the complex of DNA and protein called chromatin) might also have a role in the development of a persistent state. On page 576, Oren *et al.*[1] examine the cellular lineages and gene-expression profiles of persister cells by using a method called DNA barcoding to trace tumour cells and their descendants. Their findings illuminate the role of non-genetic, reversible mechanisms in resistance to chemotherapy for a range of tumours from different tissues.

The authors analysed cell divisions in human lung cancer cells grown *in vitro* that have a mutation in the gene encoding the epidermal growth factor receptor (EGFR). The cells were treated with osimertinib, an inhibitor of this receptor. Oren and colleagues tracked the outcomes for cellular lineages of the tumour cell line and found that 8% of the lineages gave rise to persister cells after 14 days, and 13% of the persisters resumed the cell cycle and proliferated to form cell colonies. These results show that these cycling and non-cycling persisters arise early during the course of treatment, and that they evolve from separate cell lineages.

To characterize the molecular mechanisms associated with cycling and non-cycling persister cells, the authors developed a system that they call Watermelon, to simultaneously trace each cell's lineage, proliferation status and transcriptional state (Fig. 1). To determine whether the persister state was due to a genetic, irreversible property of the persister cells, the authors re-exposed the persister cell population to osimertinib after a pause in treatment. They found that cells from both cycling and non-cycling populations reacquired drug sensitivity, suggesting that

a non-genetic, reversible mechanism underlies persistence.

The authors assessed gene expression using the method of single-cell RNA sequencing at different time points during a two-week treatment, and compared these signatures in cycling and non-cycling persisters. The cycling persistent state was uniquely characterized by the upregulation of defence programs that produce antioxidant molecules — including expression signatures characteristic of the metabolism of the antioxidant glutathione, as well as production of the protein NRF2, which is a transcription factor induced in response to oxidative stress. Moreover, the expression of several genes that are NRF2 targets correlated with lineages that had a large number of descendant persister cells, and the genetic engineering of cells to deplete a negative regulator of NRF2 resulted in an increase in the fraction of persisters that were cycling.

Osimertinib treatment induced the formation of reactive oxygen species (ROS), which can cause oxidative stress. At the end of treatment, cycling persisters had significantly lower levels of ROS compared with the non-cycling persisters. When the authors decreased ROS levels in cells through the addition of ROS scavenger molecules, the fraction of persister cells that were cycling increased. These analyses therefore suggest that the redox state of cells has a role in the regulation of cycling persisters.

Recognizing that redox balance is linked to metabolism, the authors profiled the products of metabolism in the cycling and non-cycling persisters, and identified 56 products that differed in their abundance between these two cell populations. The authors found a greater abundance of fatty acids linked to the molecule carnitine (a result of a preliminary step in the oxidation of fatty acids) in cycling states than in non-cycling states. The authors also noted an increase in the oxidation of fatty acids as a consequence of osimertinib treatment. Modulation of the pathway affecting fatty-acid oxidation revealed that increasing or decreasing fatty-acid oxidation leads to an increase or decrease in the fraction of cycling persisters, respectively. These results support the idea that a metabolic shift in fatty-acid oxidation affects the proliferative capacity of persisters.

To test whether their observations extended beyond the model system of lung cancer, Oren *et al.* generated Watermelon models of further types of human cancer, using melanoma, lung, breast and colorectal tumours. They treated the cells with suitable inhibitors, characteristic of chemotherapies, depending on the genetics underlying the particular cancer. In most of these models, the cycling persisters showed elevated fatty-acid metabolism, antioxidant responses and NRF2 signatures compared with the non-cycling persisters, showing that the authors' findings extend to cancer types other than lung cancer.

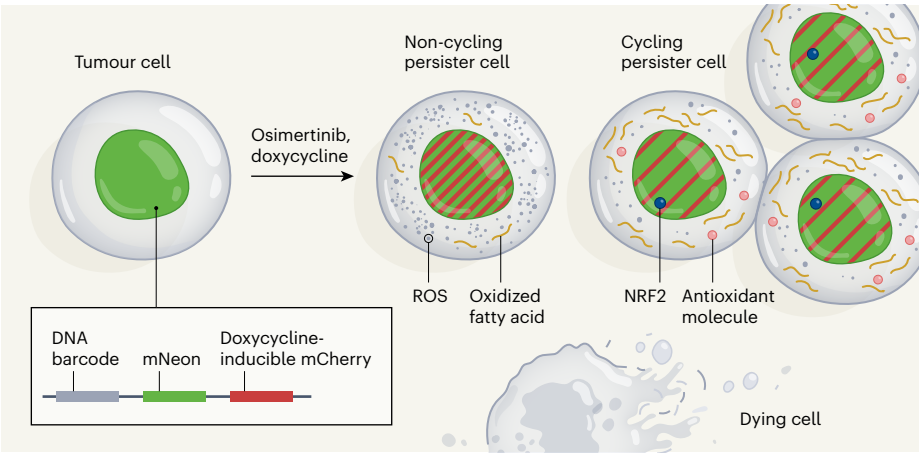

Figure 1 | A method to analyse persister cells in tumours. Oren *et al.*[1] present the Watermelon technique for analysing persisters — tumour cells that evade destruction by chemotherapeutic drugs such as osimertinib. The authors introduced an engineered DNA sequence into human tumour cells grown *in vitro*. The sequence contains a unique DNA 'barcode', which identifies the cells in that lineage. Also included are genes encoding a green fluorescent protein (mNeon), and a red fluorescent protein, mCherry, that requires the molecule doxycycline for its expression. The authors treated the cells with osimertinib and doxycycline, and analysed the surviving persister cells using single-cell analysis. The non-cycling (non-dividing) persister cells had a higher level of mCherry compared with the cycling (dividing) persisters. The persister cells contain reactive oxygen species (ROS), which cause oxidative damage. Cycling persister cells had lower levels of ROS and higher levels of oxidized fatty acids compared with the non-cycling persister cells. Cycling persister cells display hallmarks of antioxidant defences, including the expression of antioxidant molecules and the transcription factor NRF2.

These *in vitro* findings were validated using an engineered mouse model in which the animals had an inducible version of a mutant EGFR in lung tumours. After osimertinib treatment, the persister cells had a higher level of ROS and gene-expression signatures characteristic of fatty-acid metabolism compared with the cells in mice that had not received treatment. The authors also assessed gene-expression changes before and after chemotherapy in samples of cells from people with EGFR-driven lung adenocarcinoma, with melanoma driven by a mutant version of the enzyme BRAF (treated with inhibitors of BRAF and the enzyme MEK), and with breast cancer driven by a mutant version of the HER2 protein (treated with lapatinib). In all these scenarios, signatures of ROS production and fatty-acid metabolism were increased in the persister cells after treatment compared with samples of untreated tumour cells, and were higher in cycling than in non-cycling persisters.

Oren and colleagues' study fits into the wider context of current work highlighting the importance of non-genetic mechanisms in persister-cell survival and proliferation[2–4]. One major problem when studying persisters is that they are a small fraction of the initial population of tumour cells, making it difficult to characterize them by sequencing cells in bulk. The value of the authors' Watermelon method is that it enables the detailed characterization of persisters at the resolution of single cells. One future direction might be to apply similar single-cell approaches to study non-genetic mechanisms of resistance in other types of cancer, such as pancreatic[5] or prostate[6] tumours, which are fields where such research is emerging.

Understanding the dynamics of persister cells is crucial to the development of more-effective chemotherapies for cancer treatment. Previous studies found that the response pathway to the hormone oestrogen[7], which has a role in breast cancer, and the pathway related to the cell-death process termed ferroptosis[8,9] are associated with the persister state. Oren *et al.* found that, although inhibiting these pathways did decrease the amount of persister cells, there was an increase in the fraction of persisters that were cycling, suggesting that these would not be optimal chemotherapy targets.

By contrast, the authors report that inhibiting the pathway for fatty-acid oxidation using the inhibitor drug etomoxir resulted in a decrease in both the fraction of cells that were persisters and the fraction of the persisters that were cycling. This promising result indicates that modulation of this pathway, and genes that have functions related to this pathway, might be worth considering in the development of new treatment strategies.

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Political science

A bridge across the democracy–expertise gap

Mark E. Warren

An innovative algorithm provides a way of fairly selecting representative individuals for citizens' assemblies to learn about and deliberate on certain topics. Such groups hold promise for closing the gap between democracy and expertise. **See p.548**

There is a growing gulf between experts and citizens. Distrust in science is on the increase, as are conspiracy theories that challenge evidence-based decision-making. Populist attacks on institutions that provide expertise for democratic societies and processes – administrative agencies, universities and research organizations – are on the increase, facilitated by social media. Can we strengthen democracy while also ensuring that governance benefits from expertise? On page 548, Flanigan *et al.*[1] present a way of fairly and democratically selecting representative groups of citizens tasked with advising on issues that often combine politics and expertise. As supplements to the conventional institutions of electoral democracy, these bodies show promise as a means of bridging the democracy–expertise gulf.

Citizens' assemblies, the term used by Flanigan and co-authors, are a form of deliberative minipublic, the term I use here: bodies of 20–500 ordinary citizens selected near-randomly, through a process often known as sortition, and convened to learn, deliberate and make recommendations to decision makers and sometimes to the broader public (Fig. 1). They achieve three things that more-familiar institutions of democratic government do not[2].

First, because members of deliberative minipublics are selected to mirror a relevant public (they are descriptively representative of the public), they do a better job of representing groups that tend to be under-represented in elected bodies (such as legislatures), or in processes for which participants self-select (such as public hearings, petitioning and lobbying). Second, because a few ordinary citizens are acting as representatives of other citizens, the public tends to like and trust these bodies, probably because they are non-elitist, and not invested in professional politics. Third, deliberative minipublics integrate expertise, because members are tasked with learning about an issue, hearing from experts and advocates, and then deliberating over recommendations.

There is abundant evidence[3,4] that, when supported in well-designed processes, ordinary citizens can integrate expertise with moral, value-based and political considerations. On 'hot' issues (such as abortion, climate change and Brexit), deliberative minipublics' demographically representative samples of citizens tend to be less polarized than are advocates and elected representatives. This is in part because the selection process does not over-represent what are known as motivated reasoners – people who select information to support a pre-conceived position.

Flanigan and colleagues focus on the composition of deliberative minipublics. They propose and test an algorithm that maximizes fairness in selecting members by equalizing the probability of selection. Why is this important? As political entities, deliberative minipublics must be viewed as legitimate representative bodies by the broader public, if they are to bridge the democracy–expertise divide. Although research remains patchy, evidence[5] suggests that their legitimacy, as perceived by the broader public, is driven by their being representative of people who are 'like us' – underscoring the political value of such descriptive representation.

Our current understanding is that people like deliberative minipublics in part because they represent ordinary citizens, and not elites with political agendas. As such, people are more likely to trust the results obtained[5]. Furthermore, recommendations delivered by these citizens' assemblies often have greater impact on the public than does the same information delivered by experts[4]. To achieve this kind of legitimacy, those who organize deliberative minipublics must ensure the credibility of the selection processes.

But this is easier said than done. Deliberative

FABIO DE PAOLA/ALAMY

Figure 1 | Members of Climate Assembly UK, a citizens' assembly on climate change. Citizens' assemblies are a form of deliberative minipublic, in which 20–500 individuals who are representative of the demographics of a broader public are near-randomly selected to learn about, deliberate on and make recommendations on certain topics. Flanigan *et al.*[1] devised an algorithm to select individuals for citizens' assemblies fairly and in a way that ensures assemblies are demographically representative.