expression of the proteins PD1 and CD39. By contrast, the IGRP-specific CD8 T cells in the pancreas exhibited more-differentiated characteristics — low levels of TCF1 and high levels of PD1 and CD39. TCF1 is essential for the establishment and long-term maintenance of memory CD8 T cells because it promotes cellular self-renewal[6,7].

Stem-cell-like populations expressing high levels of TCF1 have been observed during T-cell responses to acute infection, chronic infection and tumours[6,8–10]. Moreover, this population of T cells can self-renew and also 'seed' the more-differentiated effector T cells and the pool of memory cells. In these cases of chronic infection and cancer, programmed functional limits are applied to the differentiated effector cells, leading to T-cell exhaustion. Gearty and colleagues' findings show echoes of this pattern, establishing that the development of type 1 diabetes involves a differentiation process in which cells — called autoimmune progenitor cells — that have high levels of expression of TCF1 then transition into effector T cells, called autoimmune mediator CD8 T cells, with low levels of TCF1 expression. These cells are initially located in the pancreatic lymph node. They then move into the pancreas, where they differentiate further and target the pancreatic tissue, causing disease, a change probably driven by their activation through antigen recognition.

The authors showed that animals given autoimmune progenitor cells expressing high levels of TCF1 developed type 1 diabetes, whereas animals given autoimmune mediator cells that had low levels of TCF1 expression did not develop the condition (probably because these cells were unable to persist long enough to cause sustained tissue damage in the pancreas). The transferred autoimmune progenitor cells generated not only autoimmune mediator cells, but also a population of self-renewing autoimmune progenitor cells that expressed high levels of TCF1. When these newly generated autoimmune progenitor cells from diabetic mice were transferred to other animals, the recipient mice developed type 1 diabetes. Blocking the exit of β-cell-specific autoimmune mediator CD8 T cells from the pancreatic lymph node resulted in an eventual loss of disease-causing autoimmune mediator CD8 T cells in the pancreas. These data show that the autoimmune progenitor cells act as a self-sustaining reservoir in the pancreatic lymph node, and are the source of the disease-causing autoimmune mediators.

Notably, studies of other animal models that report a similar type of self-renewing T-cell progenitor population in the context of chronic antigen exposure (such as chronic infection and cancer) indicate that such cells exhibit signs of exhaustion; they are called precursors of exhausted T cells (T_{PEX} cells)[8,9,11]. Surprisingly however, despite the sustained response of CD8 T cells observed in type 1 diabetes, the autoimmune progenitor cells identified by Gearty *et al.*, expressing high levels of TCF1, retained their functionality. Moreover, the autoimmune mediator cells arising from this population were highly functional. Despite some higher than normal expression of inhibitory receptors, particularly for the cells in the pancreas, the autoimmune mediator cells expressed low levels of TOX, which is a key marker of exhausted CD8 T cells[2,4]. Analysis of the gene-expression profiles of the autoimmune progenitor cells revealed a transcriptional signature that is distinct from those of either conventional memory CD8 T cells or T_{PEX} cells.

Gearty and colleagues' study suggests that the mechanisms that help to limit CD8 T-cell responses in chronic infection and cancer do not apply in type 1 diabetes, or, at least, not in the animal model studied. Two major questions stemming from the study are whether this autoimmune progenitor population is a common driver of sustained autoimmune CD8 T-cell responses and, if so, why a program of exhaustion is not initiated in these cells under conditions of chronic exposure to the self-antigens that these cells recognize.

Answering these questions might aid efforts to develop new treatments to stem the tide of disease-mediating CD8 T cells. The authors suggest that a drug that could block the exit of such CD8 T cells from the pancreatic lymph node might be a promising therapy for type 1 diabetes. For this to be effective, however, treatment would need to start soon after initiation of the generation of CD8 T cells that can recognize the self-antigens. The molecular signature of the autoimmune progenitor cells, being so different from those of conventional memory T cells and T_{PEX} cells, might allow the cells to be selectively eliminated or an exhaustion program to be induced in them, halting the disease-causing immune response. On the flip side, understanding how these autoimmune progenitor cells evade the exhaustion program might offer insights that could be used in developing sustained, antigen-specific responses to cancer.

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Condensed-matter physics

Lost magnetism pinned on atomic rotations

Georg Woltersdorf

Crystal-lattice vibrations reveal the mechanism by which laser pulses can strip a metal of its magnetism. The vibrations absorb the angular momentum of electrons in a sample, allowing it to demagnetize. **See p.73**

More than two decades ago, physicists noticed a curious thing about thin magnetic films of nickel: their magnetization was reduced almost immediately when the metal was hit with extremely short, intense pulses of light[1]. In general, materials are magnetic when the intrinsic angular momentum (or spin) of each electron aligns parallel to that of its neighbours. Because electrons carry an electric charge, this angular momentum gives rise to a magnetic moment similar to the one that arises when an electric current flows through a wire loop. So when the nickel demagnetized rapidly, researchers were understandably puzzled about what happened to the angular momentum. Writing on page 73, Tauchert *et al.*[2] have found the answer to this long-standing question, showing that the vibrational modes of nickel's crystal lattice carry a large fraction of the lost angular momentum.

Since the original report that nickel could be demagnetized with light, several experiments

have attempted to understand the physics responsible for this effect, which is present in all magnetic metals[3–6]. However, most of these studies have used techniques that are sensitive to only the electron spin — researchers were able to show that the angular momentum was lost from the spin system, but they could not determine precisely where it went. What they needed was a technique to directly track the flow of angular momentum in the crystal lattice on an ultrafast timescale.

To overcome this problem, Tauchert *et al.* carried out an experiment analogous to one that was first reported in 1915 by Albert Einstein and Wander Johannes de Haas, who showed that a magnetic object rotates mechanically when its magnetization is reversed[7]. The size of the magnetic moment generated by the angular momentum of electrons is determined by the electron's charge-to-mass ratio (gyromagnetic ratio). And because the electron's mass is very small, the sizeable magnetic moment results in only a tiny angular momentum — making Einstein–de Haas measurements very challenging, particularly for the timescales at which the demagnetization in nickel occurs.

Tauchert and colleagues found a solution by examining the lattice dynamics of a single crystalline film of nickel using a technique known as ultrafast electron diffraction. They induced demagnetization by exposing the sample to 100-femtosecond-long laser pulses (1 fs is 10^{-15} s) and observed a response consistent with a long-lasting population of lattice vibrations, known as phonons, that oscillated in a plane perpendicular to the initial magnetization. These phonons appeared within one picosecond (1 ps is 10^{-12} s) of the light hitting the sample.

Phonons are the possible modes of vibration of the periodic crystal lattice and represent collective excitations. In some ways, phonons are to sound waves what photons are to light waves. Intriguingly, the phonons that Tauchert *et al.* observed also had an angular momentum — the atoms rotated around their equilibrium positions in a plane perpendicular to the magnetization axis defined by the electron spins. These results strongly suggest that the spin angular momentum that was lost during demagnetization was equivalent in magnitude and direction to that of the emergent phonons. On timescales longer than tens of picoseconds, these excitations are expected to make the whole sample rotate slightly.

The authors accounted for the angular momentum of the phonons by focusing on the initial stage of the process in which phonons are generated. Through experiments, simulations and theory, they concluded that the phonons quickly absorb the angular momentum of the electrons, causing the entire sample to rotate at a later stage (Fig. 1). In this picture, the time required for the sample to demagnetize is related to the time needed to excite the motion of the atoms.

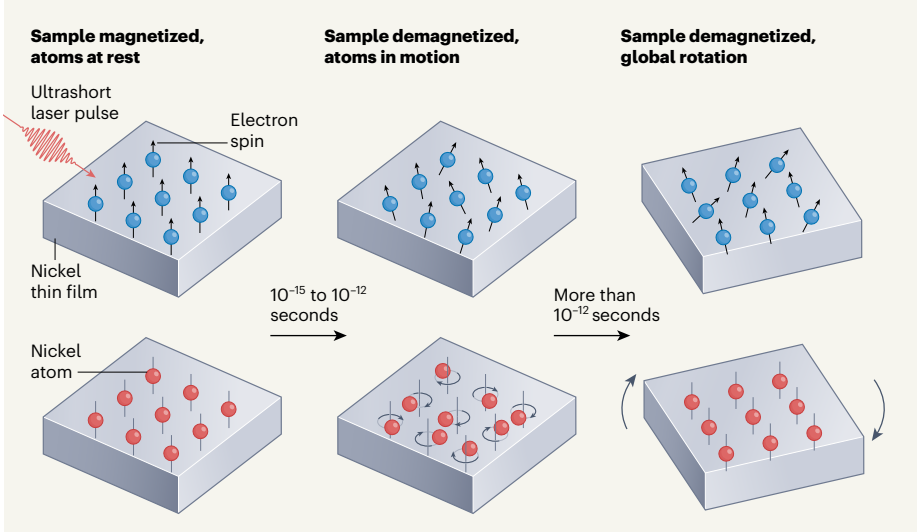

Figure 1 | Demagnetizing a magnetic material with light. A laser pulse lasting 100 femtoseconds (1 fs = 10^{-15} s) excites the electrons in a thin film of nickel, which is magnetic. The electrons (positions shown in blue in the top row) have an intrinsic angular momentum (spin), and these spins are aligned when the sample is magnetized. Within hundreds of femtoseconds, the laser pulse induces the emergence of phonons, which are collective vibrations of the atoms in the crystal lattice (equilibrium positions of nickel atoms shown in red in the bottom row; curved arrows indicate rotation around these positions). In reality, the amplitude of these vibrations is around only 1% of the distance between neighbouring atoms. Tauchert *et al.*[2] showed that the angular momentum of the electrons is absorbed by these phonons, allowing the spins to misalign, which corresponds to a demagnetization of the sample. On timescales longer than tens of picoseconds (1 ps = 10^{-12} s), these lattice excitations are expected to cause a slight rotation of the sample.

Tauchert and colleagues' experimental results can be understood in the framework of a widely adopted phenomenological model of demagnetization[4]. The data are also consistent with results reported previously in another realization of the Einstein–de Haas experiment that used X-ray diffraction[8]. That experiment showed evidence of waves moving through the material at a terahertz frequency, displacing atoms in a direction perpendicular to their propagation. These waves, which are known as shear waves, emerged within picoseconds of the light pulse hitting the sample, and were interpreted as evidence of a direct transfer of the spin angular momentum to the rotation of the whole system. But Tauchert and co-workers' observations of phonons on a sub-picosecond timescale suggest that there is an intermediate step in which the spin angular momentum is first transferred to the rotational dynamics of the lattice. On a timescale of a few picoseconds, these dynamics evolve towards shear waves with longer wavelengths than those appearing initially.

The strength of Tauchert and colleagues' work lies in providing a comprehensive atomistic picture of the ultrafast Einstein–de Haas effect that illustrates the role of phonons in optically induced demagnetization. But the study is also valuable from a technological perspective. For example, the physics of demagnetization enables ultrafast magnetization reversal of certain materials[9] and induces the emission of ultrashort spin-current pulses in magnetic multilayers[6,10]. Both of these properties might find useful applications in spintronics at terahertz frequencies. Spintronics is a type of electronics that uses the properties of an electron's spin in addition to its charge.

Moreover, the work clearly shows the key role of phonons as carriers of angular momentum during ultrafast demagnetization in materials that occur naturally. But artificial stacked structures comprising layers just a few atoms thick are also known to host ultrafast spin currents[5,6,10]. And because such currents are well characterized in layered systems and highly relevant for applications, Tauchert and colleagues' results might inspire future efforts to tailor materials, sample geometry and photon energy to maximize the electron spin-current amplitude that can be achieved in a magnetic material undergoing demagnetization by minimizing the role of phonons. Perhaps most importantly, the results reported by Tauchert and co-workers might help to refine our theoretical understanding of how electrons, photons and phonons interact in magnetic materials when, and shortly after, they are exposed to intense and ultrashort laser pulses.

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Genetics

Important genomic regions mutate less often

Jianzhi Zhang

Genomic regions that are crucial for the viability and reproduction of the model plant *Arabidopsis thaliana* are enriched with molecular features that are associated with a reduced rate of mutation. **See p.101**

Salvador Luria and Max Delbrück made a profound discovery in 1943 that won them a Nobel prize, shared with Alfred Hershey, 26 years later. What they found was that bacterial mutations that confer resistance to a virus arise at the same rate, regardless of whether the virus is present[1]. That the generation of mutations (a process called mutagenesis) is blind to its consequence has since become an established principle of genetics. Monroe *et al.*[2] report on page 101 that, in stark contrast to this tenet, the rate of mutation in the model plant *Arabidopsis thaliana* is lower in genomic regions that are functionally more important, and in regions where mutations are more frequently harmful.

By analysing thousands of mutations collected in mutation-accumulation experiments, the authors find that the mutation rate is 58% lower inside genes than in regions immediately outside them, and 37% lower in essential genes (those indispensable for viability or fertility) than in non-essential genes. Furthermore, the authors observe a negative correlation between the proportion of mutations in a gene that are deleterious and the mutation rate of the gene.

Monroe *et al.* are not the first to describe such apparently advantageous patterns of variation in the rate of mutation across a genome. For example, a previous study[3] reported that highly expressed genes in the bacterium *Escherichia coli* have relatively low mutation rates. This trend has been suggested to be an evolutionary 'risk-management' strategy[3], because the detriment imposed by a mutation tends to increase with the expression level of the mutated gene[4]. Similarly, another study[5] proposed that gene expression in the human testes is regulated to optimize gene-specific rates of mutations that are transmitted to the next generation. However, the results of both of these studies have been contested, owing to confounding factors in mutation-rate estimation, and a lack of viable mechanisms[6–8].

What mechanisms cause crucial genomic regions to mutate less in *A. thaliana*? Monroe *et al.* noticed that the mutation rate of a given genomic region (in the study, a stretch of 1,000 nucleotide bases) is correlated with several genomic features. Among these are the percentage of nucleotides in the region that are guanine or cytosine, and epigenetic features of the region — molecular modifications that affect gene activity without changing the DNA sequence. These include various modifications to histone proteins that bind to DNA and affect gene regulation, DNA replication and DNA packaging. Monroe *et al.* propose that these genomic features and (especially) epigenetic features together form part of the machinery that is shaped by natural selection to reduce mutagenesis of important genomic regions.

The evolutionary selective pressure for mutagenesis-reducing machinery should be weak, because the machinery does not directly affect the fitness of the organisms that carry it. Rather, it affects the fitness of their offspring, owing to differences in their numbers of newly generated mutations[9]. In organisms such as *A. thaliana* that reproduce by selfing (the union of male and female sex cells from the same organism), the strength of selection for this machinery approximates the number of deleterious mutations per individual per generation that the machinery prevents[9,10]. Monroe *et al.* estimate that, in the face of genetic drift (random fluctuation of frequencies of genetic variants in a population), a machinery that lowers the mutation rate of essential genes by 30% must influence at least one-third of all coding sequences of all essential genes in *A. thaliana* for it to be established by natural selection. Hence, a mutagenesis-reducing machinery is unlikely to have emerged through adaptive evolution unless it has large and broad effects.

The suppression of mutagenesis in important genomic regions could, in theory, originate

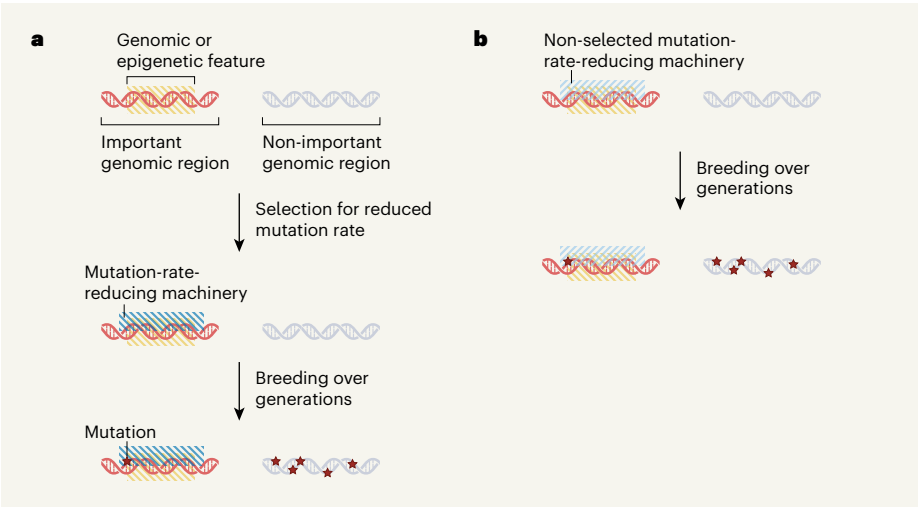

Figure 1 | Routes to lower mutation rates in more-important genomic regions. Monroe *et al.*[2] analysed mutations in the model plant *Arabidopsis thaliana*, and found that genomic regions important for plant viability and reproduction mutate less often (show reduced mutagenesis) than do other regions. This variation in mutation rate could originate in one of two ways. **a**, If a genomic feature or an epigenetic feature (a modification that affects gene activity without changing the DNA sequence) is present at important genomic regions, but not at non-important regions, natural selection could drive the emergence of a mutation-rate-reducing machinery that is associated with the feature. This would reduce the number of mutations that occur in the important regions over multiple generations. **b**, Alternatively, the association between the feature and reduction in mutation rate could be intrinsic or a by-product of some other biological processes, without selection.