

of the Exo1 nuclease. Using DSB substrates generated *in vivo* that require lengthy resection for repair, the authors followed the processing of the ends under normal conditions, or when Sae2, Sgs1 and/or Exo1 were absent.

They find that Sae2, in complex with Mre11 and its partners, initiates end processing to form the first intermediates. Next, either Exo1 or Sgs1 plus another nuclease — possibly Dna2 — resect the ends to give the required 3' tails (Fig. 1). When both of these second-stage end-processing pathways are defective and only Sae2 is active, a ladder of fragments, corresponding to incremental cleavages of 50–100 nucleotides, is seen, and end processing and homologous recombination are in general as defective as in the most severe mutant forms of homologous recombination. Thus, processing by Sae2, and by Mre11 and its associates, prepares the DSB ends for subsequent resection by either Exo1 or Sgs1.

The implications of these findings are wide-ranging. When mutated, the human RecQ helicases BLM, WRN and RECQL4 (and possibly RECQL5) have been implicated in genomic instability, a predisposition to cancer, and ageing. The defects caused by these mutations are thought to result from an inability to control the outcome of a recombination event during the late stages of homologous recombination. Consequently, inappropriate recombination events occur, and failure to resolve the intermediates properly leads to disease-associated mutations referred to as loss of heterozygosity. In light of the latest findings^{1–3}, we must consider the possibility that defective end processing, even if it is normally mediated by several pathways, could lead to incomplete repair of a DSB, with little regard for complementarity between the two strands and so leading to mutations and rearrangements.

As with all major advances, the findings^{1–3} raise more questions than they answer. The studies focused on recombination during mitotic cell division — the basic cell-division cycle that produces most cells in the body. Does regulation of end processing differ between meiosis and mitosis? What controls which resection pathway — that mediated by Exo1 or by Sgs1 — is used? Is it decided according to whether the break is caused by a cellular process or external DNA damage, the context of the damage, or the stage of the cell cycle at which it occurs?

And lastly, what are the effects of mutations in human EXO1? This nuclease would be expected to have a crucial role in repairing DSB damage. But unlike human RecQ helicases, EXO1 has not been linked to disease. It is possible that, in humans, the RecQ helicases have a more prominent role in DSB end processing than EXO1 and so the effects of mutations in the gene encoding this latter nuclease are more subtle. EXO1 mutations might be one of many factors that increase the predisposition to cancer or lead to infertility, which is associated with abnormal meiosis. The relative contributions of

the human RecQ helicases and EXO1 to DSB end processing are still to be defined. ■

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SOLID-STATE PHYSICS

Recipe for spin currents

N. P. Ong

Generating currents that rely on the spins of electrons to make electronic devices requiring less power is both desirable and daunting. A neat way of creating such currents eases that task.

The field of spintronics — spin electronics — seeks to harness the spin of electrons in metals and semiconductors in order to perform tasks that are, at present, routinely carried out by electrons' charge. Spintronics offers a promising path to achieve further reduction in both the size and power consumption of solid-state devices. The past few years have seen many ingenious experiments¹ clarifying the basic principles that govern the creation and manipulation of spin currents — the flow of electrons with a net spin polarization. On page 778 of this issue, Uchida *et al.*² introduce the 'spin Seebeck effect' as an especially elegant way of generating spin currents from a spin-voltage source that can be maintained across a distance of roughly 1 cm at room temperature.

The ordinary Seebeck effect refers to the appearance of a voltage when the ends of an electrically insulated wire are held at different temperatures (Fig. 1a, overleaf). The temperature gradient drives a heat current that is carried by electrons to the cooler end. Because the wire is electrically insulated, there is a backflow of electrons driven by a finite gradient in the chemical potential, μ — the energy of the most energetic electrons in the wire. The situation is analogous to using a fan to pile up water at one end of a fish tank. The current of surface water flowing downwind is balanced by a backflow driven by the pressure gradient in the water. At steady state, the water level in the tank (the analogue of μ) has a tilted profile. Likewise, μ exhibits a tilted profile in a temperature gradient (Fig. 1a), and the voltage observed is the difference in μ at the two ends. This thermoelectric voltage can be used to generate electricity, and is a vital source of energy in space satellites. The reverse effect, known as the Peltier effect, is used to cool materials ranging from microchips to rare wines.

The experiment carried out by Uchida *et al.*² extends the Seebeck effect to spins. In a ferromagnet — in contrast to non-magnetic metals, such as copper and platinum — the density of spin-up electrons greatly exceeds that of spin-down electrons at thermal equilibrium. A key point in the field of spintronics is that, in a non-equilibrium situation, the chemical potential of the spin-up electrons, μ_{\uparrow} , can be made to deviate substantially from that of spin-down electrons, μ_{\downarrow} . The different gradients in μ_{\uparrow} and μ_{\downarrow} then lead to distinct spin-up and spin-down currents flowing in the metal. The difference in chemical potential, $\mu_{\uparrow} - \mu_{\downarrow}$, is called spin voltage.

Several experiments¹ have investigated spin currents driven by a spin voltage that is maintained across relatively short distances. For example, when an electrical current flows from a ferromagnet into copper, both the spin-up excess and spin voltage persist in the copper over about 500 nm before vanishing. In their experiment, Uchida and colleagues obtained a spin voltage that extends over a macroscopic distance of 6 mm. They applied a temperature gradient to a thin film of a nickel–iron ferromagnet, and showed that μ_{\uparrow} and μ_{\downarrow} display distinct tilted profiles. This results in more spin-up electrons accumulating at, say, the cooler end, and more spin-down electrons at the warmer end. Hence, the spin voltage has opposite signs at the two ends (Fig. 1b).

To prove that this is indeed the case, Uchida *et al.* allowed the spin voltage to drive a spin current into a platinum film deposited across one end of the nickel–iron film. As shown in Figure 1c, the temperature gradient enables more spin-up than spin-down electrons to accumulate at the cool end of the ferromagnet (spin-up is here defined to be in the direction of the applied magnetic field). In turn, the higher μ_{\uparrow} implied by the excess spin-up population

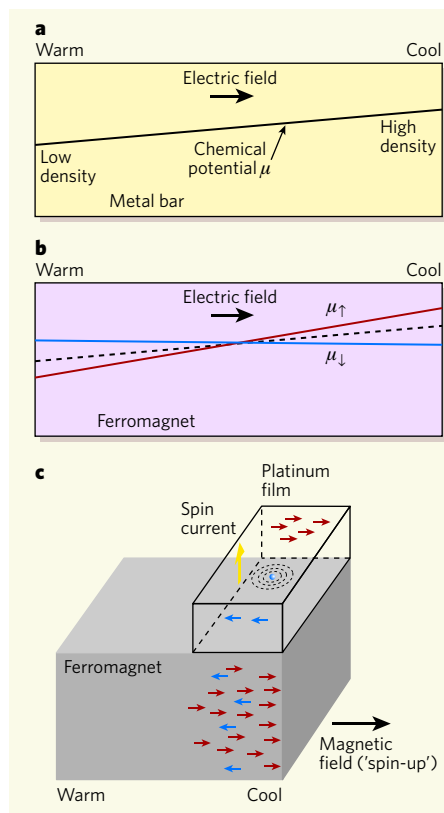


Figure 1 | The spin Seebeck effect. **a**, In the ordinary Seebeck effect, a temperature gradient in a metal bar causes more electrons to accumulate at the cool end, producing a tilt in the chemical potential (μ), which is observable as an electric field. **b**, Uchida *et al.*² extend the Seebeck effect to spins. In a ferromagnet, the temperature gradient results in an excess of spin-up electrons at the cool end, and an excess of spin-down electrons at the warm end. Their respective spin-chemical potentials, μ_{\uparrow} and μ_{\downarrow} , have tilt profiles of opposite signs (solid lines), the average (dashed line) giving the electric field. **c**, The spin Hall effect. The excess of spin-up electrons (red arrows) at the cool end of the ferromagnet drives a spin current that flows vertically into the platinum film (yellow arrow). Here, spin-up means that the direction of the spin is parallel to the magnetic field, and thus points to the right. By spin-orbit coupling, electrons 'see' a weak magnetic field circulating around a charged impurity (circles around blue dot). Scattering from the charged impurity causes spin-up electrons to accumulate preferentially on the far face of the platinum film, whereas spin-down electrons (blue arrows) end up on the near face. The imbalance is observed as a Hall voltage difference between the two faces.

drives a spin current into the platinum film. The decay of this spin current leads to the appearance of an electrical signal through the spin Hall effect^{3,4}, which enables spin currents to be detected using a sensitive voltmeter.

To understand the spin Hall effect, one can track an electron as it enters the platinum film and scatters off a charged impurity (Fig. 1c). The spin-orbit interaction — the interaction between an electron's spin and its motion — imparts a left-right asymmetry to the scattering

process. In the rest frame of the electron, the charged impurity rushing towards it constitutes a current filament, so the electron 'sees' a weak magnetic field circling the filament. This non-uniform magnetic field imparts a force on the electron along a direction that depends on its spin orientation^{3,4}. The net result is that spin-up electrons are pushed to the right of the impurity whereas spin-down electrons are pushed to its left.

In effect, each impurity acts like a spin filter that selectively kicks electrons to one side or the other, depending on their spin. As shown in Figure 1c, the excess spin-up population in the incident beam results in more charge accumulating on the far face than on the near face of the platinum film. The voltage difference between the two faces is observable as a Hall signal. The asymmetric scattering of electrons is especially large in materials with a high atomic number, such as platinum. Following its prediction^{3,4}, the spin Hall effect was first observed by applying purely optical techniques to semiconductors^{5,6}, and was later detected electrically in metals^{7,8}.

In a series of tests, Uchida *et al.*² convincingly show that the Hall voltage in the platinum film arises from the spin voltage. The Hall signal in

the platinum film tracks both the magnitude and the direction of the magnetization in the nickel-iron film. Moreover, by moving the platinum film along the length of the nickel-iron film, they show that the spin voltage varies linearly over the 6-mm length of the sample. In demonstrating that the spin Seebeck effect can produce a large, calibrated spin-voltage source that can be 'tapped' anywhere along the length of the ferromagnet, Uchida and colleagues have added an important tool to the spintronics toolbox. ■

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NEUROSCIENCE

Brain's defence against cocaine

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Long-term exposure to cocaine changes the organization of synaptic connections within the addiction circuitry of the brain. This process might protect against the development and persistence of addiction.

Neurons modify their structure and communication with other neurons in response to experiences. Such experience-dependent neuroplasticity is crucial for survival because it allows learning from, and responses to, changes in the environment. But the cellular mechanisms that mediate this process can also be co-opted by drugs of abuse. Reporting in *Neuron*, Pulipparacharuvil *et al.*¹ describe how some of the chemical, structural and behavioural changes in neurons that are induced by repeated exposure to cocaine are regulated at a molecular level.

Drug addiction is characterized by compulsive drug seeking. It resembles a chronic relapsing disorder in which the addict resumes taking drugs after a period or periods of abstinence. Human and animal studies indicate that the recalcitrant nature of addiction results from drug-induced stimulation of reward-related learning processes in the brain. The pleasure-producing effects of the drug trigger cellular and molecular processes that are normally activated by natural rewards such as food and sex. Repeated exposure to an addictive drug

leads to a long-lasting associative memory of its rewarding properties through experience-dependent neuroplasticity. In effect, drug-seeking behaviour becomes hard-wired in the addict's brain, and the persistent memory trace is easily reactivated by drug-associated environmental stimuli, such as the sight of drug paraphernalia.

Along the dendritic processes of a neuron, morphologically specialized structures called dendritic spines receive most of the excitatory signals from other neurons through synaptic junctions. These spines are considered to be a primary cellular site for mediating the synaptic plasticity that is thought to underpin memory formation². One regulator of the density of excitatory signals on dendritic spines is the gene transcription factor MEF2 (ref. 3). When active (dephosphorylated), MEF2 favours elimination of dendritic spines, and when inactive (phosphorylated) it allows spine formation^{3,4}.

Repeated exposure to cocaine and other psychostimulants increases the number of dendritic spines on medium spiny neurons