as a whole (the 'majority vote') is given by approximately 1.5ϵ — so the bias of the whole system is greater than that of any individual qubit. The majority function can be computed 'reversibly' by a permutation of the eight possible sequences of the three bits (000, 001, …, 111) such that one of the bits inherits the higher bias of the whole system and so is colder than it was before. The other two bits then pick up the excess entropy (Fig. 1a).

Closed-system experiments implementing this bias amplification have been performed previously using NMR[9,10], but the need for continuous ancilla resupply precludes a closed-system solution on a large scale. Instead, entropy must be pumped out of the computation qubits into an ambient heat bath[11], an approach known as heat-bath algorithmic cooling (Fig. 1b). What Baugh *et al.*[1] have achieved is an experimental demonstration of such a procedure. They take three hot qubits from a heat bath, put them in three computation nuclei, and then amplify the bias of one of these by a factor of 1.48 — remarkably close to the theoretically predicted performance of 1.5.

This is a significant first step along what will surely be a long experimental journey, leading, it is to be hoped, to heat-bath algorithmic cooling that can reach far lower temperatures on many more qubits. It may also be possible, even in the short term, to test a crucial aspect of open-system cooling: the use of continuous entropy pumping to achieve temperatures lower than those possible in a closed-system device. Specifically, in a closed three-qubit system, bias cannot be amplified by more than a factor of 1.5, whereas in an open system, a limit of 2 can be approached[12] by repeatedly recomputing the majority after exchanging the two 'used' (high-entropy) qubits for fresh ones from the heat bath (Fig. 1c). The modest gap between these two limits is a precursor of a much larger separation in many-qubit devices: a three-qubit open-system experiment exceeding an amplification of 1.5 will therefore be a notable milestone. ■

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CELL BIOLOGY

Silenced RNA on the move

Ralf Dahm and Michael Kiebler

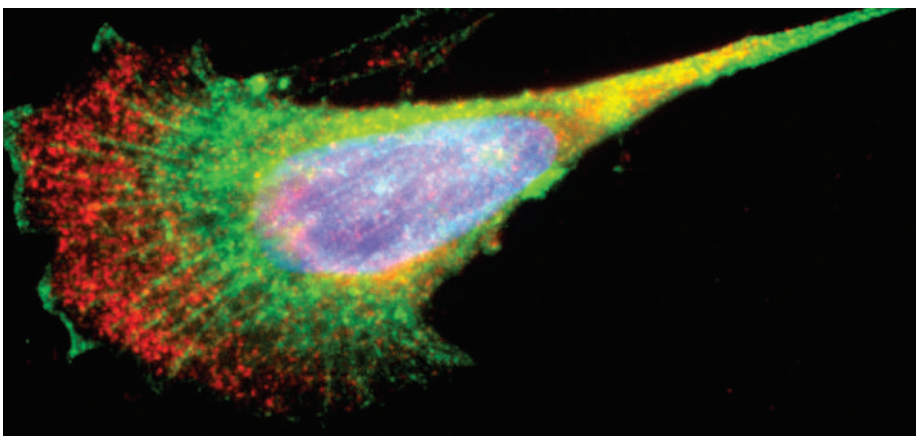
Proteins are often produced at their site of action, but the RNAs from which they are made must be kept inactive until they reach the right spot. It seems this 'silencing' of RNA is linked to its transport around the cell.

Almost all cells possess 'compartments' that enable them to separate different biological tasks. Neurons, for example, have dendrites that receive input from other cells, axon hillocks that integrate the information, and axons that transmit signals to other neurons. A key mechanism that cells use to create this functional subdivision is the localization of specific messenger RNAs (mRNAs) to distinct cellular domains[1], which allows the cells to fine-tune gene expression in both space and time. But for mRNA localization to divide up a cell effectively, synthesis of the encoded protein must be repressed until the mRNA arrives at its site of action[2], otherwise the protein will be made and begin to act all along the journey[3]. This strongly implies that there must be a tight coupling between RNA transport and repression of protein translation. In this issue, Hüttelmaier *et al.* (page 512)[4] provide the first evidence of a direct link between the two processes.

The authors studied the localization of β-actin mRNA in migrating cells. During their journey, cells extend protrusions in front of them to explore their path. These projections are generated by actin proteins polymerizing into long filaments that push the cell's membrane outwards. The β-actin mRNA is transported to the leading edge, so that the huge amounts of actin required for filament growth can be produced quickly and locally to establish cellular asymmetry (or polarity). Fibroblast cells, which proliferate around wounds and move inwards to fill in the lesion crater, are a classic example of migration (Fig. 1). This migration behaviour can be conveniently exploited in cell culture to dissect the molecular mechanisms underlying the polarization and directed migration of cells.

Previous work from the same laboratory[5] identified a short nucleotide sequence (the 'zipcode element') that is necessary and sufficient to move β-actin mRNA to the protrusions of fibroblasts and other migrating cells including neuroblastoma cells. The protein ZBP1 binds to the zipcode sequence, and is essential for this localization in fibroblasts and for the formation of dendritic filopodia, the precursors of synapses (the contact points between neurons)[5]. Now, Hüttelmaier *et al.*[4] demonstrate that ZBP1 also represses the translation of β-actin mRNA, both *in vitro* and in intact neuroblastoma cells. Moreover, neuroblastoma cells lacking functional ZBP1 do not repress the translation of β-actin. However, when ZBP1 is reintroduced into these cells, translation is again repressed. Together, these experiments show that RNA transport and translational regulation are more intimately linked than previously anticipated.

But what occurs to switch the mRNA from the translational 'off' state that prevails during transport to the 'on' state once the RNA–protein complex reaches its destination? A close inspection of the ZBP1 sequence revealed a potential SH3-binding motif. Such motifs can serve as docking sites for the non-receptor tyrosine kinase Src — an enzyme that adds phosphate groups to other proteins. Hüttelmaier *et al.* show that Src does indeed phosphorylate ZBP1 (on tyrosine 396) *in vivo*, and that the phosphorylation makes ZBP1 much less able to bind to β-actin mRNA *in vitro*. Similar mechanisms regulate the



A. WELLS

Figure 1 | A migrating fibroblast cell. β-actin mRNA (red) localizes to the fibroblast's leading edge. β-actin protein is shown as green, and the nucleus is stained blue.

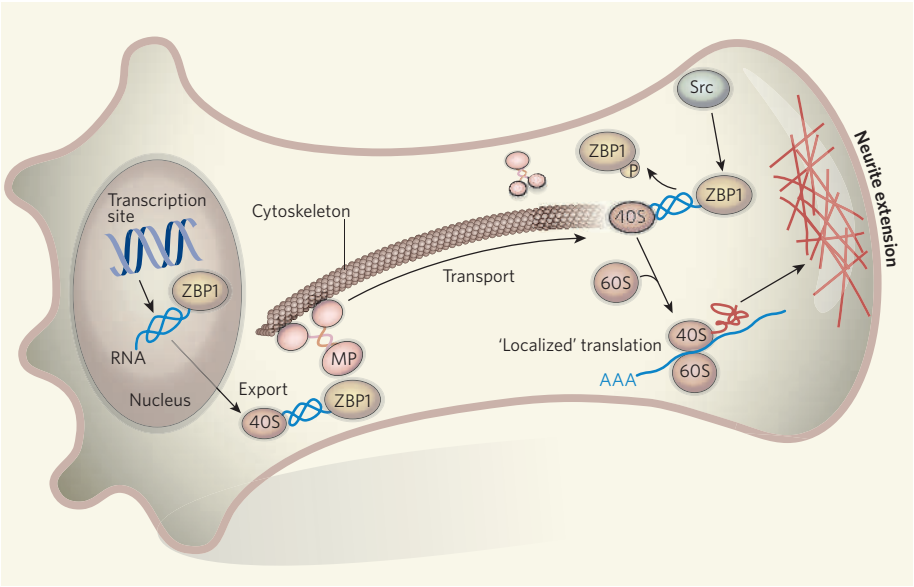


Figure 2 | Regulation of localized β-actin mRNA translation in a polarized neural cell. Hüttelmaier *et al.*[4] propose that the ZBP1 protein controls the transport of β-actin mRNA and its subsequent translation into β-actin protein. ZBP1 associates with the β-actin mRNA in the nucleus and is exported to the cytoplasm. Here, the ZBP1–β-actin RNA complex binds to a motor protein (MP) and is transported along the cytoskeleton, the cell's internal scaffolding, to the periphery. During transport, ZBP1 prevents the mRNA from being translated into protein. When the ZBP1–β-actin RNA complex reaches its destination near the plasma membrane, ZBP1 is phosphorylated (P) by the non-receptor tyrosine kinase Src. This releases the mRNA, allowing the 40S and 60S subunits of the ribosomes to assemble and synthesize β-actin protein (red). The monomeric β-actin protein then assembles into the 'subcortical actin cytoskeleton', which pushes the leading edge onwards.

activity of other RNA-binding proteins[6]. So to investigate whether phosphorylation of ZBP1 modulates its regulatory role in translation, the authors used cells lacking wild-type ZBP1 and introduced into them a mutant ZBP1 that cannot be phosphorylated. This mutant ZBP1 could no longer repress translation of the β-actin mRNA, suggesting that phosphorylation by Src is crucial for translational regulation by ZBP1.

Where does this regulatory step occur? Hüttelmaier *et al.* next used fluorescence imaging to watch ZBP1 and Src in neuroblastoma cells. The two proteins came together only at the base of filopodia and in growth cones — motile, actin-rich structures that lead the way for outgrowing neurites. To obtain evidence that this interaction is functionally significant, the authors examined neurite outgrowth in cells lacking ZBP1. These cells have much shorter projections than usual, but adding ZBP1 back into the cells allowed them to grow normal-looking neurites. Adding the mutant, phosphorylation-incompetent ZBP1 did not produce normal outgrowths, and markedly reduced the amount of newly synthesized actin at the cell's periphery.

This is the first evidence that tyrosine phosphorylation of ZBP1 induces *de novo* synthesis of β-actin in a cellular compartment. It implies that ZBP1 could control a range of cellular processes, including cell migration and the formation of cellular polarity, especially the establishment of neuronal connections. The findings suggest a multi-step model for the regulation of mRNA transport and translation (Fig. 2): in the nucleus, RNAs that will act at specific locations associate with corresponding RNA-binding proteins ('nuclear priming'). Once assembled, these 'transport-competent' RNA–protein complexes are exported into the cytoplasm[7], where they associate with the cytoskeleton (the cell's internal scaffolding) and are transported to the cell's periphery with the help of molecular motors[8]. During their journey, the transcripts are translationally repressed by their protein partners, but on arrival at their destination they under- go a spatially controlled de-repression to initiate translation in specific compartments of a cell.

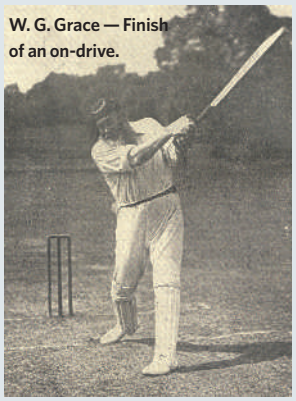
This study generates many interesting questions that now need to be addressed. First, the mechanism of how ZBP1 controls translation is unknown, although the authors present preliminary evidence that unphosphorylated ZBP1 may inhibit the joining of the 40S and 60S subunits of the ribosome (the protein synthesis machinery). Second, it remains to be shown that the phosphorylation of ZBP1 regulates its RNA-binding capacity in an intact cell — there might be additional mechanisms that control ZBP1 function. Third, we do not understand how β-actin mRNA translation is restricted to the leading edge of a fibroblast or to the growth cones of developing neurons, rather than occurring all round the cell's periphery. Is Src kinase localized in a more restrictive manner than generally assumed, or is it spatially regulated? Fourth, how does this

50 YEARS AGO

"Laboratory design" — It was decided to carry out a survey of the use actually made of space and services by scientists working in reasonably well-provided laboratories... Differences in the [bench] lengths used by scientific and experimental officers were small; it was found for these grades that about 12ft. of benching satisfied one man's requirements for 97 per cent of the time... A finding of some interest was that for 57 per cent of a scientist's time and 33 per cent of an assistant's time no bench was in use at all.
From *Nature* 26 November 1955.

100 YEARS AGO

Great Batsmen, their Methods at a Glance. By G. W. Beldam & C. B. Fry; Pp. xiv+716; illustrated by 600 Action photographs. Price 21s. net.



W. G. Grace — Finish of an on-drive.

Each of the many batsmen pictured has been photographed in one or more characteristic attitudes before, during or after the striking of the ball, and after a careful study of every picture, Mr Fry has set down his own interpretation for the guidance of the reader... W. G. Grace, for example, is shown in twenty-six different attitudes, and all have some lesson to tell. In the photograph reproduced we have the finish of an on-drive, in which the turn of the body has aided powerfully in giving full effect to the stroke. The eyes are still looking at the spot where the ball was when it was struck. The whole series of photographs prove that all great batsmen follow the ball with their eye right up to the moment of striking.
From *Nature* 23 November 1905.

50 & 100 YEARS AGO

newly discovered function of ZBP1 contribute to biological and pathological processes involving cell migration? Such processes occur, for example, during embryonic development, infiltration of tissues by immune cells, wound healing and metastasis. Finally, does ZBP1 also act as a translational repressor in polarized neurons? If so, it will be exciting to discover whether it is involved in processes such as neurite outgrowth, axon guidance and synaptic plasticity, which underlie learning and memory. ■

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CONDENSED-MATTER PHYSICS

Focus on the Fermi surface

Peter Littlewood and Šimon Kos

The electrical resistance of some manganese oxides takes a tumble when they become magnetic. Close examination confirms the interplay of conduction electrons and lattice vibrations that contributes to this effect.

Certain manganese oxides (manganites) exhibit an intriguing effect known as 'colossal magnetoresistance'. Below a certain critical temperature, these materials become ferromagnetic — showing the spontaneous alignment of electron spins that accounts for the magnetic attraction of materials such as iron — and this is accompanied by a drastic reduction in electrical resistance. On page 474 of this issue, Mannella and colleagues[1] describe the electronic properties of a two-layer manganite compound, $La_{1.2}Sr_{1.8}Mn_2O_7$ (LSMO), revealing that the interaction of electrons and lattice vibrations known as phonons is crucial to colossal magnetoresistance. The results also bring to light unexpected similarities between the electronic structures of manganites and superconducting copper oxides.

In a metallic material such as a manganite, electrons fill quantum-mechanically allowed energy states singly from the lowest possible energy upwards. (This is a consequence of the Pauli exclusion principle, which holds that no two electrons may share the same quantum state.) The energy of the most highly occupied state is known as the chemical potential, or Fermi energy. The electronic energy states in a solid with a periodic lattice structure also have a well-defined momentum; when components of these momenta in the three spatial dimensions are plotted against each other, the occupied states form a characteristic shape bounded by a so-called Fermi surface. Only electrons in states near the Fermi surface — those with the highest momenta — contribute to conduction. According to a central tenet of quantum mechanics, known as Heisenberg's uncertainty relation, how sharply defined these energy states are is a measure of the degree to which electrons scatter on the lattice or on each other. So a good metal, with a low electrical resistance (little scattering), will have a sharply delineated Fermi surface.

Mannella and colleagues[1] provide the first experimental observation of the Fermi surface in a manganite. The technique they use, photoemission spectroscopy, is based on the photoelectric effect, in which light striking a metallic surface behaves as if it were a particle, knocking out a loosely bound electron. The electron's momentum and energy can be probed directly using this method, and the photoelectric effect has been a workhorse of experimental condensed-matter physics since it was first explained by Albert Einstein 100 years ago (for which he won the Nobel Prize in Physics in 1921).

The authors show that the Fermi surface of LSMO becomes more sharply defined when the material is cooled into the ferromagnetic state, indicating that its resistance has fallen. The result fits in with our understanding of colossal magnetoresistance as the suppression, induced by the onset of ferromagnetic order, of an interaction between electrons and phonons (the quanta of lattice vibrations)[2] that increases resistance. This bundling of electron and lattice properties can itself be treated as a physical entity moving through the lattice — a 'quasiparticle' known as a polaron. Scanning tunnelling microscopy measurements of LSMO support this picture[3], showing images of polarons trapped by occasional impurities.

Mannella and colleagues' results also indicate that the spectral weight of the sample (loosely, the proportion of the total number of energy states that exist at the Fermi surface) is very small, explaining why these states have not been observed previously. In addition, the measured energy spectrum at the Fermi surface is not isotropic, but depends strongly on the direction: electrons propagate readily (albeit with a velocity five times smaller than expected) in a direction that is diagonal to the square lattice of manganese atoms, but poorly along the axes of the lattice.

The reduced spectral weight and velocity seem to imply that, even in the metallic state, in which conduction electrons supposedly move freely throughout the lattice, electrons and phonons are interdependent. The results are puzzling, because at low temperatures manganites such as LSMO are good metals with an isotropic conductivity. The shape of the Fermi surface itself — with large parts that are nearly parallel, or 'nested' — supplies one possible interpretation. Nesting provides a channel through which an electron can be scattered between different parts of the Fermi surface; in this case it is scattered by a phonon, but in general it could also be scattered by magnetic fluctuations, should these exist. Scattering would reduce the electronic spectral weight around the Fermi energy and induce a gap in the energy spectrum.

The spectrum measured by Mannella *et al.* is very similar to that of the mysterious 'pseudogap' phase seen in high-temperature cuprate superconductors. This intriguing fact suggests that such a gap is a generic feature of the oxides of transition metals — rather than being a facet only of cuprate superconductors, as had been assumed. A further widespread belief is that phonons play no role in the high-temperature superconductivity seen in cuprates, despite the fact that interactions between electrons and phonons underlie conventional, low-temperature superconductivity. But it has been shown[4–6] that phonons affect various properties of the electrons in these superconductors, especially in the pseudogap phase. Mannella *et al.*[1] provide yet another incentive to examine the role of phonons more carefully. ■

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