frequency of oscillation in step with their own excitation, as two connected pendula do in the familiar classroom experiment. Here, it suffices to couple the cyclotron and the axial motion through the minute inhomogeneous magnetic field of a tiny nickel wire.

To measure the thermal distribution of the electron's energy of axial vibration requires a two-step 'pump–probe' operation. Because any axial energy value is correlated with a shifted cyclotron frequency, the probability of an axial excitation — its 'strength' — is mapped onto the particular strength of cyclotron excitation when the electron is irradiated with microwaves of a frequency correspondingly shifted off resonance. The quantum of cyclotron excitation is tiny compared with light quanta, but much larger than those of axial excitation: the electron absorbs at most one of them when randomly jumping to its first cyclotron-excited state after a pump microwave 'pump' pulses is applied.

The effective cooling of the electron is revealed in the power spectrum of noise in the circuit (inset; derived from ref. 1): a notch in the spectrum shrinks as the feedback increases; the frequency at which the notch appears is the resonant frequency of the electron between the caps.

When the microwave pump radiation is varied in steps around the cyclotron resonance, the resulting spectrum of measurements shows how likely it is that the electron has acquired one quantum of cyclotron motion. This spectrum mimics a Boltzmann distribution, whose width directly displays the 'temperature' of the electron's axial vibration. The measurements show that, when the strength of the feedback is increased, the width of the distribution shrinks down — the lowest temperature reached in their experiment was 850 mK. Singling out and cooling electrons gives a means of measuring, with very great accuracy, fundamental quantities in quantum electrodynamics, such as the ratio of the electron's spin to its magnetic moment. In a heroic effort by theorists, this number has been calculated to ten decimal places, and so far, no significant discrepancy has been found between it and the value measured in experiments. But it is quite possible that even higher precision may reveal a deviation — or even that the value for the electron's antiparticle twin, the positron, is different. This is crucial in the matter-antimatter relationship that is at the very heart of our understanding of matter.

D’Urso and colleagues’ feedback cooling may well contribute to dramatically reducing errors in these measurements, furthering our never-ending struggle for higher accuracy of observation and refined modelling of nature.

Peter E. Toschek is at the Institut für Laser-Physik, Universität Hamburg, Jungius-Straße 9, D-20355 Hamburg, Germany.

e-mail: toschek@physnet.uni-hamburg.de


Stem cells

Fusion brings down barriers

Alexander Medvinsky and Austin Smith

It remains uncertain how tissue-specific stem cells could generate the mature cell types of another tissue. In one instance, where bone-marrow-derived stem cells repair damaged liver in mice, cell fusion is the answer.

The respective merits of embryonic versus adult stem cells for treating diseases have been widely discussed, in both the popular press and the scientific literature. In particular, reports that the developmental potential of adult stem cells might be greater than previously supposed have aroused strong interest and controversy. The papers by Wang and colleagues and Vassilopoulos and co-workers on pages 897 and 901 of this issue mark a further turn in the debate. These authors confirm that stem cells derived from adult bone marrow can repair damaged liver tissue in mice — but not by converting directly into liver cells, as might be expected if the stem cells could change their developmental ‘destiny’. Instead, cell fusion with the host liver is responsible for bringing down the barriers between bone marrow and liver.

Many tissues and organs in adult mammals contain reserves of stem cells to ensure...
their long-term anatomical and functional maintenance. Stem cells are very few in number, but have both a high proliferation potential — allowing their lifelong renewal — and the capacity to generate fully mature, tissue-specific cell types. These strategic cell reserves are recruited in response to physiological demands or tissue damage.

Adult organs have generally been considered to be closed cell communities, reflecting their distinct developmental origins. Thus it was assumed, for instance, that stem cells from the brain are restricted to producing brain-specific mature cell types. Recently, however, the dogma of ‘tissue fidelity’ has been challenged. There have been reports that, following transplantation, cells derived from bone marrow can turn into liver, muscle, nerve and other specialized cell types. Conversely, it has been claimed that stem cells from the brain can produce blood or muscle. Such reports have given rise to the concept that stem cells from adult tissues are not constrained by their ancestry, and have the ‘plasticity’ to alter their destiny.

But some investigators have been sceptical about these findings. A key issue is the true identity of cells produced through ‘tissue conversion’. To show that a certain cell type originated from a transplanted stem cell, the presence of both a marker gene from the donor and a tissue-specific protein must be demonstrated. But to show this unambiguously is technically demanding. And it is even more difficult to show that a particular cell, even if it appears to be specialized, actually functions in a tissue-specific way. In addition, ‘converted’ cells often occur singly, a fact that is difficult to reconcile with a stem-cell origin, which is expected to generate clusters of progeny.

These concerns appeared to be addressed in a study showing that mice with a fatal metabolic liver disease — a vital enzyme, fumarylacetoacetate hydrolase (Fah), is missing in these animals — can be ‘rescued’ by the transplantation of purified blood stem cells. Histological examination revealed massive areas of healthy, donor-derived liver tissue. This observation was reproducible and the livers were demonstrably functional, as the animals survived. So blood can produce liver — but how? Do the blood stem cells directly generate liver cells (Fig. 1a)? It seems not. A well-known way by which cells can change identity is through cell fusion. In hybrid cells produced by fusion, molecules from one fusion partner reprogramme gene expression in the genome of the other partner. Fusion can occur spontaneously in vitro — this was shown for the first time in the 1960s, and again more recently in reports that also indicated that hybrid cells can function in vivo. Wang et al. and Vassilopoulos et al. now show unequivocally that the cells that build healthy liver tissue in Fah-deficient mice contain both donor and host genetic markers. Cells with such a genetic constitution can only have arisen by in vivo fusion. So, the donor cells effect functional rescue by delivering their genome, which includes the Fah gene, into pre-existing liver cells (Fig. 1b). In the resulting hybrids, liver-cell molecules dominate over blood-cell factors, so that liver gene expression is activated and blood gene expression is silenced.

The ancients recounted the myth of Prometheus, whose damaged liver was continuously regenerated. In this tale — and in liver regeneration in general — it is not stem cells that are required, but rather the proliferation of mature liver cells. In the new work of the contribution of the hybrid cells seems to depend on this regenerative context, and on the space created by degeneration of the diseased host liver. (This may explain why, in healthy liver, transplanted bone-marrow cells yield only single liver cells.) The liver may also be a particularly favourable setting for hybrid cells, because normal liver cells often carry several copies of each chromosome. Hybrids, too, generally have an additional set of chromosomes (Fig. 2).

One important remaining question is exactly which cells fuse with the host liver; there is no evidence that it is the stem cells themselves. Instead, it seems more likely that differentiated progeny of the stem cells, such as blood cells known as macrophages, are responsible, because a contribution to the liver is seen only after the donor stem cells have populated the animals’ blood system. It will be essential to identify the precise fusion partners in order to optimize any clinical applications. Another question is whether the Fah gene is already active in certain donor-derived blood cells, or whether it is activated after fusion. Furthermore, the extent to which gene expression throughout the genome is reprogrammed in hybrids — and whether this is prone to error, as is the case with cloning — will require meticulous investigation.

Another remarkable observation reported by Wang et al. is that some cells in the rescued liver contain only two copies (a pair) of each chromosome. How could fusion occur without an increase in chromosome number? The most probable explanation is that hybrid cells undergo a ‘reduction division’, in which an entire set of paired chromosomes is lost. Such reduction divisions would conceal fusion history (Fig. 2), introducing a further confounding factor to the investigation of tissue conversion.

The issue of stem-cell plasticity in its pure form — that is, whether a stem cell from one tissue can transform into a different tissue type — will remain open for some time. Last year’s discovery of multipotent adult progenitor cells (MAPCs) added a further dimension. These cells can produce various mature cell types in isolation, and therefore without fusion, but how do MAPCs arise in

Figure 1. Possible mechanisms by which transplanted blood cells could transform into liver cells. a. Direct conversion of donor blood cells into liver cells, induced by the liver environment. A converted cell and its daughters contain only donor chromosomes. (Marker chromosomes are depicted, by which donor, green, and host, brown, can be discriminated.) b. Fusion of donor blood cells with resident liver cells. A hybrid cell and its progeny generally contain both donor and host chromosomes. The indicated hybrid cell underwent reduction division, reducing the number of chromosome pairs to the norm (see Fig. 2). The studies by Wang et al. and Vassilopoulos et al. demonstrate scenario b.
the first place? They seem to develop over time in culture, possibly because they become liberated from tissue-restricted gene expression. Could it be that fusion between distinct tissue-specific cell types in the starting population creates hybrids that reprogramme to become MAPCs?

Our new understanding of how blood cells produce liver should have an impact on research into the use of bone-marrow transplantation for treating certain genetic disorders: gene transfer through in vivo fusion now seems a distinct possibility. But the major applications of regenerative medicine seem likely to be delivered through embryonic and tissue-specific adult stem cells.

Alexander Medinsky and Austin Smith are at the Institute for Stem Cell Research, University of Edinburgh, King's Buildings, Edinburgh EH9 3JQ, UK. e-mails: a.medinsky@ed.ac.uk austin.smith@ed.ac.uk


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news and views

Telling the tale of the first stars
Timothy C. Beers

HE0107 — 5240 is a star in more than one sense of the word. Chemically, it is the most primitive object yet discovered, and it is at the centre of debate about the origins of the first elements in the Universe.

Late last year, the discovery of the most iron-deficient star yet identified, HE0107 — 5240, was announced. This star has a measured abundance of iron less than 1/200,000 that of the Sun. Its significance is that it seems to be a relic from the early Universe, and astronomers are now busy considering how to interpret it.

In this issue, three groups — Bonifacio et al., Umeda and Nomoto, and Schneider et al. — present various interpretations of HE0107 — 5240. Each of these contributions centres on whether this star exhibits properties that might reveal the likely range of mass that should be associated with the so-called population III stars — objects that are presumed to have formed shortly after the Big Bang, and which are thought to have produced the first elements heavier than H, He and Li, as well as the "first light" in the Universe. Population II stars are objects that formed after population III stars and which incorporated the metals created by this previous generation. Our Sun, and other (younger) metal-rich stars in the Galactic disk, are referred to as population I objects.

To the astronomer, metals include all elements heavier than H, and they are thought to be produced only by nuclear reactions that take place during the lifetimes, or at the deaths, of stars. Stars such as our Sun have inherited the net production of metals by all of the previous generations that lived (and died) before it. Stars with the lowest observed abundances of heavy elements, such as HE0107 — 5240, must therefore have been born before other stars, because the gas clouds from which they formed had only the slightest traces of these heavy elements. So, regardless of the outcome of debate about the nature of the very first stars, HE0107 — 5240 remains chemically the most primitive object yet discovered, and is a crucial "laboratory" for tests of the origins of the first elements in the Universe.

Despite the apparent simplicity of the composition of HE0107 — 5240, which to date has yielded the detection of nine elements (H, C, N, Na, Mg, Ca, Ti, Fe and Ni), the new papers present a dizzying array of possible explanations for their origin. By comparison, other extremely low-metallicity stars, with Fe abundances near 1/1000 the solar level, such as CS22892 — 052 (ref. 5) and CS31082 — 001 (refs 6, 7), show evidence of roughly 40–60 individual elements, most arising from the so-called rapid neutron-capture process, which accounts for the production of roughly half of all elements heavier than Fe. Beyond its Fe deficiency, the singular feature of HE0107 — 5240 is that its measured abundance of C, relative to Fe, is about 10,000 times the observed ratio of these elements in the Sun, the largest such "over-abundance" ratio ever seen. The N abundance ratio is also greatly enhanced, though only by a factor of 200. The other detected elements exhibit ratios similar to those in previously identified metal-deficient stars.

Explanations put forward for the composition of HE0107 — 5240 fall into three main categories. First, that it is indeed a low-mass, population III star that formed out of gas of zero metallicity, and has had its present surface abundances altered. Possible mechanisms for changing the observed atmospheric abundances of HE0107 — 5240 include internal mixing of elements produced by nuclear burning in the star itself, and the acquisition of metals produced by later generations of stars during its passage through an already enriched interstellar medium, or — as now seems more likely — even in the cloud of its birth, from the contribution of material from later supernovae.

The second possible explanation is that it is a low-mass population II star, of an extreme form, and that the observed elemental abundances directly reflect the yields of species from supernova explosions of massive (more than 200 times the solar mass) population III stars that were incorporated into the gas from which HE0107 — 5240 formed.

Third, as above, except that the observed abundances reflect the yields of one or more supernova explosions of population III stars of "normal" mass (20–25 solar masses) that were present shortly before its birth.

An important point here is that each of...