relevance of the morula-enriched gene set.

Further investigation may also reveal the epigenetic mechanisms that underlie the expanded developmental potential of *in vivo*-derived iPS cells. Previous work[4–6] has suggested that DNA methylation is crucial to safeguard pluripotency against commitment to extraembryonic lineages. Although the widely used mouse ES cells and *in vitro*-reprogrammed iPS cells are functionally pluripotent, the fact that they undergo an *in vitro*-programmed lineage restriction raises provocative questions regarding the fidelity of cell-state transitions induced in cell culture, and about the accuracy of cellular models generated by differentiation or manipulation in the laboratory.

Do human pluripotent stem cells have totipotent-like potential? Human ES cells were initially thought[7] to generate trophectoderm on treatment with the protein BMP4. However, subsequent work showed that BMP4-treated human ES cells generate a subpopulation of cells that resemble extraembryonic mesoderm and do not correspond to genuine placental trophoblasts[8]. It is now thought that, rather than corresponding to an early totipotent-like state, human ES and iPS cells represent a distinct 'primed' state of pluripotency corresponding to a later stage of embryonic development than that of 'naive' mouse pluripotent stem cells[3]. This fundamental distinction between mouse and human pluripotent stem cells may greatly influence the potential to produce extraembryonic lineages. We speculate that generation of human pluripotent stem cells with similar features to mouse ES cells may improve access to extraembryonic lineages *in vitro*. Generation of real placental derivatives from human pluripotent stem cells would enable modelling of placenta-associated disorders.

Abad and co-authors' work represents a landmark for what could become a powerful strategy in regenerative medicine — tissue reprogramming *in situ*. A hallmark of limb regeneration in amphibians is the formation of a blastema, a mass of dedifferentiated proliferating cells that undergoes morphogenesis and redifferentiates to replace structures that have been lost by amputation. However, there is currently no mammalian counterpart to the amphibian blastema, although there is a growing interest in strategies to induce regenerative responses in mammals, especially humans. In this regard, *in vivo* application of the latest transgene-free reprogramming technologies, such as those using modified messenger RNA sequences[9] or a recently reported reprogramming cocktail of small molecules[10], may allow reprogramming *in situ* to proceed in a controlled manner. The growing parallels between reprogramming and regeneration should inspire the application of reprogramming technologies in living organisms for regenerative ends. ■

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ASTROPHYSICS

Super-luminous supernovae on the rise

New observations suggest that certain extremely bright supernovae are not the nuclear explosions of very massive stars. Instead, they may be ordinary-mass events lit up by a potent central fountain of magnetic energy. SEE LETTER P.346

DANIEL KASEN

Although every supernova is remarkably brilliant — at its peak, the average stellar explosion shines about a billion times brighter than the Sun — astronomers have recently discovered an astonishing class of super-luminous supernovae that outshine the ordinary ones by almost a hundredfold[1,2]. These are very rare examples of extreme stellar death, and their progenitors are unclear, although it has been tempting to associate them with the most massive stars in the Universe. On page 346 of this issue, Nicholl *et al.*[3] present data that, for certain events, point to a different origin.

The origin of ordinary supernovae has been agreed on for decades; the most common events occur when a moderately massive star (one of around 10–20 solar masses) has nearly exhausted its nuclear fuel. The stellar core, now filled with ash, cannot maintain the pressure to withstand its own gravity, and collapses to a dense, compact nugget — a neutron star — releasing enough energy in the process to blow away the outer layers in a supernova explosion.

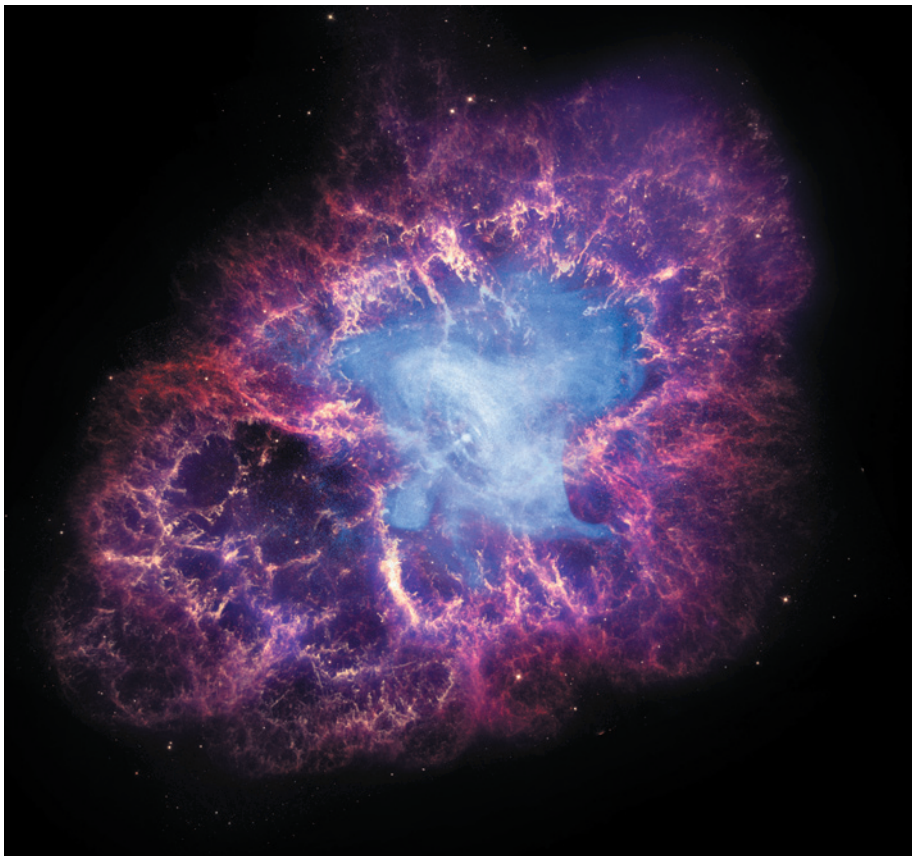
For extremely massive stars, however, a different, and much more energetic, outcome may be possible. A star initially larger than about 140 solar masses becomes so hot in its interior that pairs of electrons and anti-electrons are spontaneously produced from the thermal bath. The energy expended in making these particles depletes the pressure support, and the star becomes 'pair unstable'. The core begins to fall inwards, but this time with its fuel tank still completely full.

The outcome is, predictably, catastrophic. As the core contracts and becomes compressed, burning accelerates exponentially, and nearly all the remaining fuel is consumed within seconds. That extreme energy release completely blows the star apart, expelling a massive cloud of highly radioactive debris. The radioactive glow of the expanding cloud can be visible from more than a billion light years away.

The theory of these hyper-energetic nuclear explosions, called pair-instability supernovae (pair-SNe), was proposed[4] in the 1960s, but it was only a few years ago that astronomers found evidence of an actual event[5]. A remarkably luminous supernova, named SN 2007bi, resembled the theoretical predictions; in particular, its brightness gradually faded at a rate consistent with the half-life of cobalt-56, a radioisotope produced abundantly in pair-SNe.

The discovery excited but confused theorists. Pair-SNe are expected to occur in pristine regions of pure hydrogen and helium gas. SN 2007bi was found in a galaxy mildly polluted by chemical elements heavier than hydrogen and helium — what astronomers call metals. Theory suggests that stars containing even small traces of metals will continuously shed material in winds, losing so much mass early in their lives that they avoid the pair instability. If SN 2007bi was indeed a pair-SN, our understanding of the formation and evolution of very massive stars needed to be reconsidered.

As it turns out, there is a relatively simple test of whether a supernova is big enough to be a pair-SN. The more massive and opaque a debris cloud, the longer it takes light to diffuse



X-RAY: NASA/CXC/SAO/F. SEWARD; OPTICAL: NASA/ESA/ASU/J. HESTER & A. LOLL; INFRARED: NASA/JPL-CALTECH/UNIV. MINN./R. GEHRZ

Figure 1 | The Crab nebula. At the centre of the Crab nebula — the remnant of a supernova that exploded nearly 1,000 years ago — a spinning, magnetized neutron star is slowly injecting energy into the surrounding gas cloud, lighting it up. A similar, but more extreme, physical process may explain the super-luminous supernovae observed by Nicholl and colleagues[3]. A neutron star spinning ten times faster than the one in the Crab nebula, and with magnetic fields 100 times stronger, would inject its spin energy much more rapidly, within a few months, and shine more than a million times more brightly.

out of it. The radioactive glow of a giant pair-SN should therefore rise to its peak brightness unusually slowly, over a period of about a year[6,7]. That is several times longer than the rise of an ordinary-mass supernova. Unfortunately, astronomers did not catch the rise of SN 2007bi; they discovered it just as it was peaking.

But now Nicholl *et al.* have discovered two super-luminous supernovae that are dead ringers for SN 2007bi. This time the events were caught early, and the rise time to peak could be measured. The rise was relatively rapid, about two months, implying a moderate debris mass of only 10–20 solar masses. Their conclusion: these two new supernovae — and presumably SN 2007bi, by association — are not pair-SNe.

What could they be? One existing idea[8,9], favoured by Nicholl and colleagues, is that the emission is powered not by radioactivity, but by the activity of a spinning, highly magnetized neutron star (a 'magnetar'). In this picture, the progenitor star was not extraordinarily massive, but it was rotating rapidly, and on collapse formed a magnetar spinning nearly 1,000 times per second. The kinetic energy stored in that dense, whirling flywheel would be enormous, with the strong magnetic fields providing a mechanism to steadily transport the spin energy to the surrounding debris cloud, lighting it up[10]. This would be an extreme version of the emission seen from the remnants of some ancient supernovae (Fig. 1). Simplistic models of this process nicely explain the rise and fall of SN 2007bi and its doppelgängers[3,4].

Hints of magnetar activity have been noted[11] in a few other supernovae that reach similar peak brightnesses to SN 2007bi, but fade more rapidly after peak, perhaps pointing to a unifying mechanism for a range of super-luminous events. But other mechanisms for producing very bright supernovae are possible; for example, expanding supernova debris may encounter a dense shell of gas, and light up in a violent collision[12]. Nicholl and colleagues' data should be valuable in discriminating between different models.

Meanwhile, the pair-SNe, after a brief fling with reality, seem to have crept back into the realm of theoretical conjecture. Having failed to find a convincing candidate in their survey, Nicholl *et al.* argue that these events must be rare in the nearby Universe, less than 1 for every 100,000 ordinary supernovae. But our best chance of finding one may be to look into the very distant, very early Universe. Back

then, stars were probably bigger, and mostly free of metals. Future telescopes should be able to see a long way there; maybe they will catch a glimpse of these largest of nuclear explosions. ■

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CANCER

Killing from the inside

Lysosomes are the main degradative compartment in cells, but they are also involved in cell-death pathways. Studies using existing drugs show that lysosomes are excellent pharmacological targets for selectively destroying cancer cells.

PAUL SAFTIG & KONRAD SANDHOFF

There have been numerous efforts to identify the Achilles heel of cancer and to find ways of killing tumour cells while leaving normal cells unaffected. The development of cancer chemotherapy started in the 1940s, and our increasing understanding of cancer biology has led to ever more precisely targeted therapies. Most of these strategies target the abnormal proliferative behaviour of cancer cells. Now, writing in *Cancer Cell*, Petersen *et al.*[1] propose an alternative intracellular anticancer target — the lysosome*.

For a long time, lysosomes were misleadingly regarded as the cell's waste bin, but we now know that they are more akin to cellular stomachs. In the lysosome, macromolecules are degraded by hydrolase enzymes, including protein-degrading cathepsin enzymes, and the resulting components are released as nutrients into the cytoplasm. Importantly, lysosomes are involved in several cellular processes, such as membrane repair, pathogen defence, autophagy and signalling[2]. The lysosomes in cancer cells are more numerous, larger and have greater cathepsin activity than those in normal cells, and the release of cathepsins from cancer-cell lysosomes into the extracellular space can promote tumour progression[3].

Lysosomes are also involved in cell death — the release of certain cathepsins from the lysosome into the cytoplasm is thought to trigger death by apoptosis and apoptosis-like pathways[4]. This release occurs by a process known as lysosome membrane permeabilization (LMP), which possibly occurs following certain changes to the composition of membrane lipids and major lysosomal membrane proteins[5]. LMP can be induced by various stimuli, including reactive oxygen species and endogenous apoptotic stimuli. However, cancer cells seem to overcome this threat of death by invoking the action of the protein Hsp70, which is expressed in many tumour types. Hsp70 specifically binds to a negatively charged lipid called bis(monoacylglycero)phosphate (BMP), which is found in the membrane of vesicles in the lysosome lumen[6]. This binding activates acid sphingomyelinase (ASM), an enzyme that breaks down the lipid sphingomyelin[7], which is a typical and important component of cell membranes. Interestingly, increased ASM activity seems to support lysosomal integrity. Prompted by this observation, Petersen *et al.* hypothesized that inhibiting ASM in cancer cells would increase lysosomal fragility, LMP and cell death (Fig. 1).

It was already known that cationic amphiphilic drugs (CADs) — substances that are well established for the treatment of depression, allergies and hypertension — act as ASM modulators. At the low pH of the lysosome, the drugs interfere with the electrostatic interaction between ASM, which is cationic, and the anionic surface of BMP-rich intralysosomal membranes[8,9]. The displaced ASM is then rapidly degraded by cathepsins. Petersen and colleagues tested the effects of CAD treatment on several types of cancer cell, and found that the drugs killed the cells at much lower concentrations and shorter exposure times than was required for them to affect the viability of non-transformed cells. CAD treatment also led to reduced tumour growth in animal models. Furthermore, the authors found that cancer cells that were resistant to many other anticancer drugs were susceptible to CADs. Fascinatingly, this treatment restored the cells' susceptibility to the other drugs.

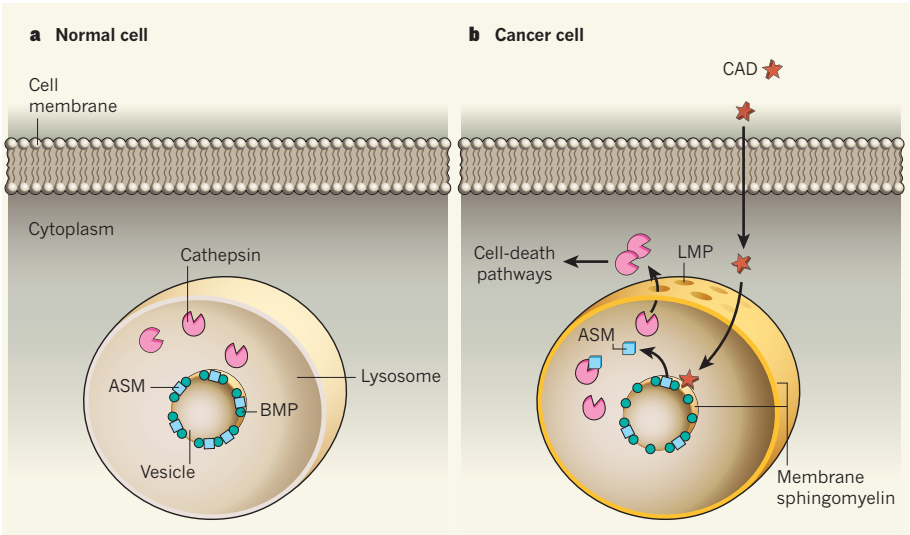

Figure 1 | Lysosomes as a therapeutic cancer target. a, The degradation of macromolecules in lysosomes is achieved by hydrolase enzymes, including cathepsins. Another lysosomal enzyme is acid sphingomyelinase (ASM), which breaks down the membrane lipid sphingomyelin. ASM is positively charged and associates with another, negatively charged, lipid called BMP, which is found in the membranes of vesicles in the lysosome lumen. **b**, ASM activity is lower in cancer cells than in normal cells, and thus sphingomyelin levels are higher. Petersen and colleagues[1] show that cationic amphiphilic drugs (CADs) selectively kill cancer cells. CADs are positively charged, so they can displace ASM from vesicular membranes such that it is degraded by cathepsins. It is possible that this blocks the residual ASM activity in cancer cells, leading to even higher levels of sphingomyelin, which may disturb membrane homeostasis and cause lysosome membrane permeabilization (LMP). This allows cathepsins to be released into the cytoplasm, triggering cell-death pathways.

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