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corrections to the electroweak theory, published[10] in 1971, that depended strongly on the mass of the heaviest of the six quarks, the top quark, and also on the mass of the Higgs boson. There was remarkable agreement between the top-quark mass predicted by LEP and the mass eventually measured by the Tevatron proton–antiproton collider at Fermilab near Chicago, Illinois, in 1995.

Eventually, the last missing ingredient of the standard model was the Higgs boson. Experiments at LEP actively searched for the elusive particle, but it became clear that an even more powerful accelerator was needed to produce it. LEP operations ended in 2000, paving the way for the installation of a new proton–proton collider, the Large Hadron Collider (LHC), in the same tunnel. The discovery of the Higgs boson was famously announced in 2012 by two LHC experiments, ATLAS and CMS. Again, its measured mass was in excellent agreement with predictions.

This is by no means the end of the story. In the original electroweak theory, neutrinos were assumed to be massless, but the phenomenon of 'mixing', in which one type of neutrino transforms into one of the other two types, proved this could not be the case. The details of the neutrino masses — which must be very small, but not zero — and the exact nature of these particles are still not known. Next-generation neutrino-beam experiments planned in Japan and the United States will explore these questions in richer detail. An upgrade of the LHC will also continue running until the early 2040s, ultimately aiming to deliver ten times more collisions than the original design.

Meanwhile, a detailed feasibility study of a Future Circular Collider is in progress at CERN. This would replicate the LEP–LHC model in a tunnel with a 90-kilometre circumference: first, an electron–positron collider would be installed to measure the Higgs boson and electroweak processes with even greater precision, and then a hadron collider would explore even higher-energy phenomena, including the production of two Higgs bosons in the same collision, at a much higher rate than that obtained at the LHC. Such experiments should reveal whether the simplest standard-model description of the Higgs boson is correct, or if there is a more complex structure to it — whether there is more than one type of Higgs boson, for example, or whether it interacts with other unknown particles.

This programme might also give clues to the nature of unseen cosmic 'dark matter', for which there is strong evidence from astronomical observations. Just as the LEP measurements were sensitive to the top quark and Higgs boson, precise measurements at future colliders might reveal the influence of as yet unknown, heavier particles. Fifty years after Gargamelle laid the foundations of electroweak interactions, and with it the standard model, a decades-long programme of rich fundamental science still lies ahead.

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Medical research

Immune cells aid therapy for Parkinson's disease

Qizhi Tang

Inflammation caused by surgical trauma limits the survival of transplanted stem-cell-derived neurons in rodent models of Parkinson's disease. Co-transplanting immune cells called regulatory T cells improves the therapy's efficacy. See p.606

Parkinson's disease is a neurodegenerative disorder characterized by a progressive loss of the neurons in the brain that produce the neurotransmitter dopamine. After decades of research, it is now possible to generate dopamine-producing neurons from human stem cells, and this technology has raised hopes that transplanting such neurons into the brains of individuals with Parkinson's disease might provide a cure[1]. However, to be effective, the transplanted dopamine neurons would need to survive the implantation procedure and avoid immune rejection. Park et al.[2] report on page 606 that more than 90% of transplanted dopamine-producing neurons die within two weeks of implantation into animals because of a profound inflammatory response induced by the trauma of the surgery. The authors point to a possible way of tackling this problem.

Park et al. show that the inflammation caused by surgery is not only directly toxic to dopamine-producing neurons, but also increases immunogenicity — the 'visibility' of the graft to the immune system. To try to quell the inflammation and reduce immune activation, the investigators turned to a group of immune cells called regulatory T (T_{reg}) cells (Fig. 1). This specialized lineage of T cells is dedicated to suppressing inflammation, constraining immune activation and promoting tissue repair[3]. Park and colleagues found that transplanting T_{reg} cells together with the stem-cell-derived neurons suppressed the local inflammatory response, promoted survival of the neurons and improved therapeutic outcomes in animal models. These results support the idea that Parkinson's disease could be treated with a composite graft that contains dopamine-producing neurons and a person's own T_{reg} cells.

The possibility of treating diseases using stem-cell-based therapies has attracted considerable attention because of the unique ability of stem cells to self-renew and to differentiate into myriad cell types. These cells can be isolated, cultured outside the body and directed to form various cell lineages by mimicking the processes that occur in the body during normal tissue development. Such advances in stem-cell technology have improved the prospect of having cells 'on demand' to replace or repair damaged tissues and organs and thereby treat a wide range of degenerative diseases. However, the immense potential of stem-cell-based therapies in regenerative medicine will only be achieved if the barriers of poor cell survival and immune rejection can be overcome.

Several strategies have been developed to reduce the likelihood of transplanted stem cells being recognized and attacked by the immune system[4]. However, 'immuno-engineering' approaches alone will probably have a limited effect, given that 90% of transplanted cells are lost even in the absence of immune rejection, as Park et al. show. Poor cell engraftment is a major challenge for many regenerative cell therapies. In Park and colleagues' study, neurons that produce the neurotransmitter GABA had levels of cell death that were comparable to those of dopamine-producing neurons after transplantation. Similarly, the poor survival of stem-cell-derived cells that are generated to

treat diseases – such as insulin-producing cells, liver cells and cardiac muscle cells – limits their therapeutic efficacy[5–8].

Many factors contribute to the dismal survival of transplanted cells derived from stem cells. These cells are typically produced in an environment with an oxygen concentration of 21%, which greatly exceeds the levels of oxygen (1–5%) in tissues in the body. The ensuing decrease in oxygen after transplantation would induce cellular stress associated with insufficient oxygen (hypoxia), leading to rapid cell death. Moreover, cells cultured with rich nutrition for weeks in the laboratory would undergo acute nutrient deprivation after transplantation. This effect could act together with the hypoxia to create conditions that are extremely stressful for cells[9]. Finally, stressed and dead cells activate inflammatory cells in the host to produce inflammatory molecules such as TNF, IL-1 and IFN-γ that can kill transplanted cells, as Park and colleagues show.

One proposed strategy to overcome cell loss is simply to transplant increased numbers of cells. In theory, transplanting ten times more cells than are needed to restore function should compensate for a 90% loss. However, injecting more cells into a confined space leads to competition for limited oxygen and nutrients at the graft site, resulting in severe hypoxia and nutrient deprivation that exacerbates inflammation and cell loss.

The authors' study indicates that T_{reg} cells could offer a powerful means of promoting the survival of dopamine-producing neurons. Several characteristics of T_{reg} cells might contribute to their effectiveness in this context.

First, T_{reg} cells suppress unwanted inflammation using a range of mechanisms. Their adaptability to the tissue environment makes them more effective than conventional anti-inflammatory and immunosuppressive drugs in a context in which the molecular mediators of inflammation and immune activation might be unknown and could vary from person to person[10]. Approaches to increase the number of T_{reg} cells have been successful in controlling neuroinflammation after stroke and traumatic brain injury, and in inflammatory neurodegenerative diseases such as motor neuron disease (amyotrophic lateral sclerosis)[11–13].

Another notable feature of T_{reg} cells is that they act locally. Co-injecting the cells with dopamine-producing neurons directly into the brain requires only 2% of the T_{reg} cells to achieve the same protective effect as would be needed if the T_{reg} cells were injected into the bloodstream. Local injection of T_{reg} cells not only concentrates the cells where they are needed, but also prevents immunosuppression occurring elsewhere in the body. Although a composite graft of dopamine-producing neurons and an individual's T_{reg} cells would increase the complexity of the therapy, the
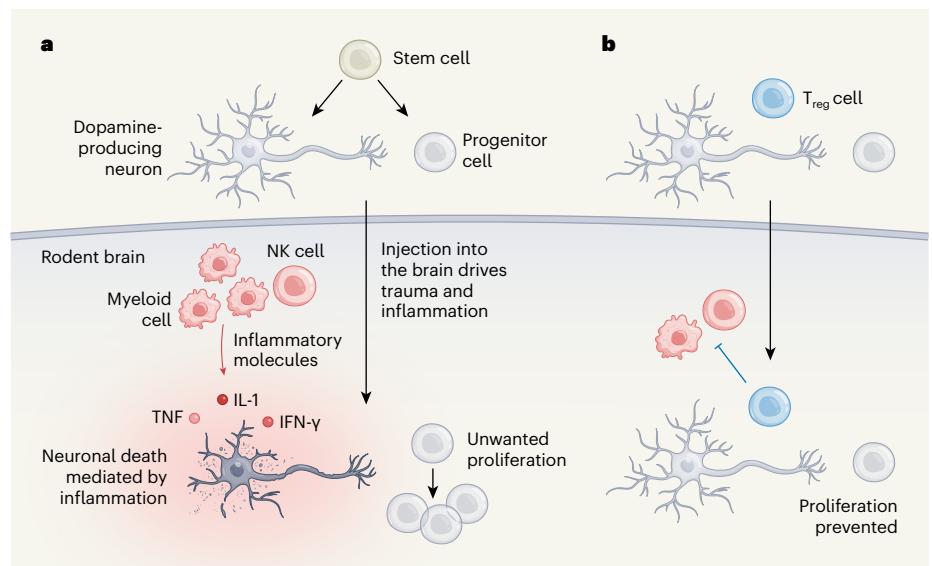

Figure 1 | Use of immune cells to treat Parkinson's disease. Park *et al.*[2] examined the survival of stem-cell-derived neurons that produce the neurotransmitter dopamine and that were transplanted into the brains of rodents in a model of Parkinson's disease. **a**, The injection trauma drives a local response associated with a rise in inflammatory cells, including myeloid cells and possibly natural killer (NK) cells, that secrete pro-inflammatory molecules such as TNF, IL-1 and IFN-γ, which can kill neurons. Progenitor cells – transplanted stem-cell-derived cells that had not differentiated fully – proliferate. **b**, Including immune cells called regulatory T (T_{reg}) cells with the injected cells dampens inflammation, aids neuronal survival and prevents unwanted proliferation.

low number of T_{reg} cells that would be needed for local injection makes this highly feasible.

Lastly, one risk of stem-cell-based therapy is that not all of the stem cells differentiate fully into the desired cell types. Any less-differentiated cells in the graft might then proliferate and interfere with the functioning of the graft and the surrounding tissue. Unexpectedly, Park *et al.* observed that T_{reg} cells constrained the proliferation of the stem-cell-derived progenitor cells – which are cells that have not differentiated fully into neurons. This effect might be related to the normal role of T_{reg} cells in regulating tissue-resident stem cells[14]. It is also possible that T_{reg} cells affect the proliferation of the grafted cells indirectly by suppressing the production of proliferation-promoting inflammatory molecules.

Park and colleagues' study shows that the survival of dopamine-producing neurons after transplantation can be improved by controlling inflammation, and provides a proof of concept for the use of T_{reg} cells in safeguarding regenerative cell therapy. Although T_{reg}-cell co-transplantation alone could not prevent the immune-cell-mediated rejection of foreign cells, this approach might be combined with other strategies, such as immunosuppression (as used by Park *et al.*), to improve therapeutic outcomes. Another possibility would be to remove the HLA proteins that identify the transplanted cells as 'foreign', and thus 'hide' them from the immune system.

The authors' results raise many questions that might be addressed in future studies. For

example, what induces the inflammation at the injection site? One possibility is that the surgical procedure damages blood vessels, causing the highly proinflammatory molecule fibrinogen to leak into the brain[15]. Could the inflammatory response be reduced by limiting the effect of the changing oxygen levels in the graft using preconditioning against hypoxia and extra nutrient provision[9]?

Could the actions of T_{reg} cells be mimicked by off-the-shelf conventional drugs, which would be easier to apply in the clinic than would T_{reg} cells? How T_{reg} cells suppress the proliferation of the progenitors is another interesting question. And what happens to the progenitor cells in the graft with T_{reg}-cell co-transplantation? Do they persist and subsequently become mature neurons? Finally, it would be of interest to assess the use of co-transplantation of T_{reg} cells to aid regenerative therapies that are being developed for other disorders, such as neurodegenerative diseases, type 1 diabetes, spinal-cord injuries, cardiovascular conditions and organ failure.

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Astronomy

Slow-beating radio waves from a long-lived source

Victoria M. Kaspi

Astronomers have uncovered a source of radio waves that pulsate more slowly than expected. Meticulous records reveal that the emission has been detected for decades, highlighting the remarkable foresight of scientists in bygone years. **See p.487**

Celestial objects change on a range of timescales, and understanding these scales is one of the most exciting areas of astrophysical research today. For instance, rapidly rotating, highly magnetized neutron stars, called radio pulsars, emit beams of electromagnetic radiation that pulse on timescales of milliseconds to several seconds, and can also vary on a microsecond scale (see, for example, ref. 1). Fast radio bursts[2] are even shorter flashes of radio waves that appear randomly across the sky, lasting tens of microseconds to milliseconds[3], whose origin is elusive at present. But astronomical timescales can also be much longer. On page 487, Hurley-Walker *et al.*[4] report a finding on a much more leisurely timescale: a radio source that pulsates with a period of 21 minutes — and that is also of unknown origin.

Radio pulsars were discovered in 1967 by then graduate student Jocelyn Bell[5]. Their pulsations are thought to originate from an effect that resembles a cosmic lighthouse: the rotation axis of the neutron star is not aligned with its magnetic axis, so when radio beams emerge from its magnetic poles, the signal rotates with the spinning star. When one of these beams crosses Earth, a radio pulse can be detected. The short periods of pulsars thus reflect the high rotation rates of these stars — in the case of ultrafast millisecond pulsars, the stars rotate as fast as the blades in a kitchen blender.

The radio emission is thought to be generated by charged particles spiralling in the intense magnetic field near the stellar poles. The motion of the magnetic field induces a powerful electric field that accelerates these particles to close to the speed of light. But this mechanism works only if the magnetic field is sufficiently strong and the rotation rate sufficiently high; if either one is not, the induced electric fields are too weak to accelerate particles enough to form a detectable radio beam.
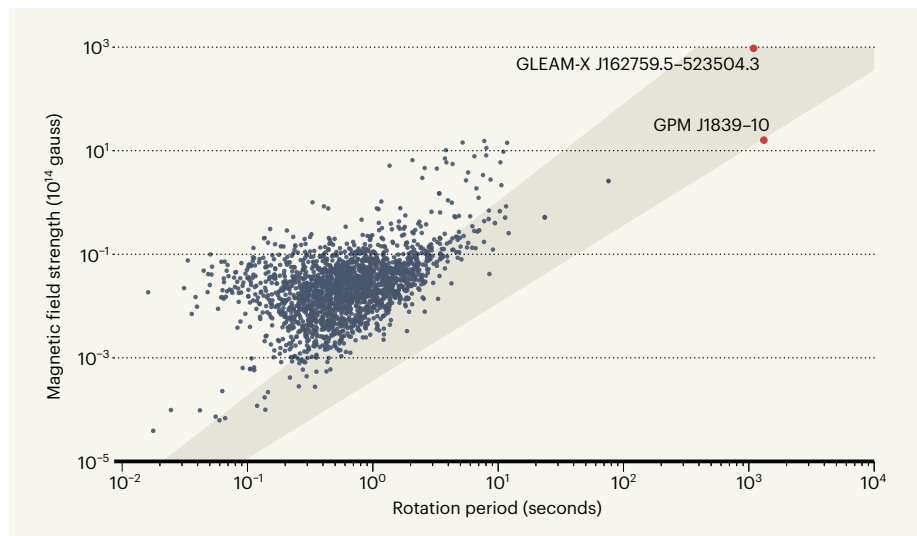

Figure 1 | A new source beyond the pulsar death valley. Various rotating celestial objects, including sources called pulsars, emit pulsating electromagnetic radiation that is thought to arise through the acceleration of charged particles as a result of the objects' intense magnetic fields. However, this explanation holds only for strong enough fields and fast enough rotation, so there is a range of these values, known as the 'pulsar death valley', which defines the plausible limits for radio emission to arise. Hurley-Walker *et al.*[4] detected a source named GPM J1839−10, which has a 21-minute rotation period that puts it beyond this range, and has been active for decades. Researchers from the same group previously observed GLEAM XJ162759.5−523504.3, a source with an 18-minute rotation period, which faded after three months[7]. (Adapted from Fig. 4 of ref. 4.)

Theorists have long defined the 'pulsar death line' as a set of values for rotation rate and magnetic field strength, below which radio pulsations cannot be generated. The exact location of the death line depends on model subtleties, so a survey of the literature yields a range of possibilities, sometimes called the pulsar death valley (Fig. 1). For many years, the zippy second- and millisecond-long rotation periods of pulsars positioned these objects comfortably on the 'safe' side of typical death lines, happily in line with theoretical expectations, although some sources have hinted that the span of the death valley might be slightly underestimated (see, for example, ref. 6).

Hurley-Walker and colleagues' surprise discovery is a pulsar, dubbed GPM J1839−10, that lies well beyond the limits of the death valley — past the farthest possible line predicted. This object is even more extreme than a source named GLEAM XJ162759.5−523504.3, which has an 18-minute period and was previously found by researchers in the same group[7]. How can particles be accelerated enough to cause radio emission if these sources rotate at a snail's pace? And if rotating neutron stars are not responsible for the emission, what exactly is its source, and how does it derive the energy required to cause the radio pulsations?

One possibility is that GPM J1839−10 is some form of highly magnetized white dwarf. As the pulsar emits radiation, it loses rotational kinetic energy. The luminosity of the emission is proportional to the star's moment of inertia — a measure of how much an object resists rotational acceleration. White dwarfs