and with functional recovery, but this effect has been ascribed to enhanced reformation of blood vessels (revascularization) and cell survival, rather than the formation of cardiomyocytes[10].

Wei *et al.* now provide new and counter-intuitive insights into the biological functions of Fstl1. Their study shows that, in the healthy heart, the protein is expressed in the epicardium, the membranous layer surrounding the myocardium, throughout development and in adult life. They also observed that heart infarction causes Fstl1 expression to be transferred from the epicardium to the myocardium, and that this shift impairs the heart's regenerative ability. Remarkably, the study reveals that re-established expression of epicardial Fstl1 can regenerate the injured heart muscle.

The investigators hypothesized that a patch releasing epicardial Fstl1, when placed onto the heart infarct, would serve as a source of Fstl1 and stimulate proliferation of the resident cardiomyocytes (Fig. 1). To test this hypothesis, they loaded collagen patches either with medium containing Fstl1 in which epicardial cells had been cultured, or with human Fstl1 purified from a bacterial protein-expression system, and sutured these to the hearts of mice that had undergone modelled myocardial infarction. Four weeks later, they observed more cardiomyocytes, higher transcription of cardiac marker genes and a greater frequency of calcium pulses (indicative of heart pumping) compared with infarcted hearts without patches. There was also less formation of fibrotic scar tissue and a better revascularization of the area. These findings suggest that such *in situ* manipulation might allow control of the fate of existing cardiomyocytes, to achieve heart regeneration without implanting cells.

This study is an inspiring example of how a developmentally conserved regulatory pathway can be mobilized to induce heart regeneration. Although more work needs to be done to determine the benefits of such an approach in large-animal models (the authors conducted a preliminary study in pigs, but it involved only six animals divided into three groups), the proposed reconstitution of epicardial Fstl1 could lead to entirely new modalities for treating heart infarction. The study also leaves us with questions about the biological phenomena responsible for the observed effects. Fstl1 is still an enigmatic protein with largely unknown properties, but with seemingly huge potential for diagnosing and treating heart disease.

One intriguing question is why infarction-induced myocardial expression of Fstl1, or even experimentally induced overexpression of Fstl1 in the myocardium, cannot induce heart regeneration, but epicardial Fstl1 applied on the patch can. The authors also find this result paradoxical. They suggest that different extents of glycosylation (the number of carbohydrate molecules — glycans — attached to the protein) that they measured for epicardial and myocardial Fstl1 reflect differences in glycan structure that affect the proteins' function. It remains to be seen whether these differences are cell-of-origin specific, how important glycosylation is for regenerative ability, and what the necessary features would be for a patch that can induce regeneration in the human heart.

Other questions arise from the combined observations that, although myocardial Fstl1 does not induce cardiomyocyte generation, it does protect immature cardiomyocytes, whereas epicardial Fstl1 on a patch enhances cardiomyocyte proliferation, but is not cell-protective. Further investigation is needed to explore whether glycosylation is a key determinant of cardioprotective versus cardiogenic effects, as proposed by Wei and colleagues. Finally, the study suggests that only very immature cardiomyocytes respond to Fstl1. The genetic signatures and the origin of the responsive cells (whether they are resident or recruited) also remain to be determined.

These questions are likely to motivate future studies. Exciting approaches are now emerging at the interface of stem-cell biology and tissue engineering. High-fidelity models of human heart tissue, combined with findings such as these, could markedly advance quantitative biological research and the clinical translation of discoveries into curative treatments for heart disease. ■

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NUCLEAR PHYSICS

Neutrons with a twist

Neutrons do not normally have orbital angular momentum. But the demonstration that a beam of neutrons can acquire this property, 23 years after it was shown in photons, offers the promise of improved imaging technologies. SEE LETTER P.504

ROBERT W. BOYD

Neutrons were discovered in 1932 by the physicist James Chadwick, and the particles continue to amaze scientists to this day. It was initially thought that neutrons were elementary particles — that is, that they were not composed of other particles. But we now know that, just like protons, neutrons are comprised of three elementary particles called quarks. Quarks have an intrinsic property known as spin angular momentum (or spin), and they endow the neutron with a spin that has a value of ½$\hbar$ (where $\hbar$ is the reduced Planck constant). On page 504 of this issue, Clark *et al.*[1] show that a free neutron can have a different kind of angular momentum: orbital angular momentum (OAM).

OAM is a broad concept in modern physics, but is usually associated with the motion of electrons around the atomic nucleus in atoms and molecules. In contrast to spin, OAM is not an intrinsic property of the electron: it can take any value of an integer L multiplied by $\hbar$, whereas the electron's spin has a fixed value of ½$\hbar$. Electron spin and OAM are analogous to Earth's rotation on its axis and its orbit around the Sun, respectively.

But OAM has also arisen in a different context: in the early 1990s, it was theoretically[2] and experimentally[3] shown that any helically phased light beam can possess OAM. It has since been established that this is true even for a single photon[4]. This is therefore another source of angular momentum for the particle, in addition to its spin (which is associated with the circular polarization of light). It is a crucial property of photons that has found applications in the field of photonics, such as the coding of quantum[4] and classical[5] information in individual photons, quantum-entanglement protocols[6] and the manipulation of small particles by optical forces[7].

In 2010, electron beams with OAM were also generated, confirming that this property is not limited to light beams[8]. Many advances in the production and use of OAM-carrying electron beams have since been reported (see

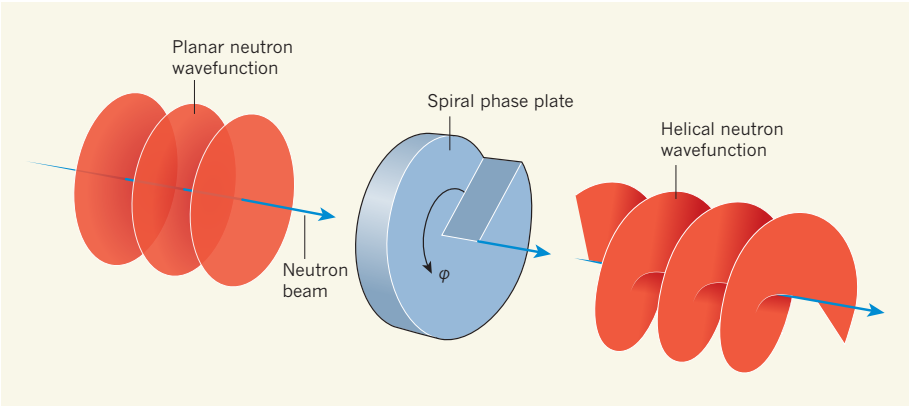

Figure 1 | Orbital angular momentum of neutrons. Clark *et al.*[1] channelled a beam of neutrons through a device known as a spiral phase plate, which modified the neutrons' original, planar wavefunctions and imparted orbital angular momentum to the particles. The wavefunction of the neutrons that emerge from the device has acquired an azimuthal phase distribution of the form $e^{iL\varphi}$ (where i is the imaginary unit, L is any integer and φ is the azimuthal angle of the plate). This phase variation causes the helical structure seen in the emergent wavefunction, which is associated with the acquired orbital angular momentum.

ref. 9 for a review). The fact that photons are not the only particles that can have OAM has opened up possibilities for fundamental studies of electromagnetic interactions and for applications such as improved electron microscopes.

Clark and colleagues' work adds neutrons to the list of particles that can have OAM. The authors generate OAM-carrying neutrons by guiding a beam of the particles through a device known as a spiral phase plate (Fig. 1). The thickness of this device varies uniformly as a function of the plate's azimuthal angle, φ (the angle measured around the circumference of the plate). The wavefunction of a neutron passing through this device acquires a phase shift that is proportional to the plate's local thickness. For appropriate values of the variation of thickness with φ, the wavefunction acquires an azimuthal phase distribution given by $e^{iL\varphi}$, where L is any positive or negative integer and i is the 'imaginary unit' (the square root of –1).

The authors fabricated several plates whose thickness distributions corresponded to various values of L, and thus generated neutron beams carrying OAM of different $L\hbar$ values. Like its spin, a neutron's OAM is a quantum-mechanical attribute. It occurs as a consequence of the helical structure of the particle's 'twisted' wavefunction when it emerges from the plate. To verify that the neutron beam had acquired OAM as it passed through the plate, Clark *et al.* used a technique known as neutron interferometry. In this approach, the neutron wavefunction was split into two paths and a spiral phase plate was placed in one of them. The two paths were subsequently combined coherently to form an output beam whose interference pattern showed the azimuthal phase distribution that the wavefunction had acquired.

Although Clark and colleagues' results are impressive, they represent only the first step in an emerging field of research. For example, in the present experiment, the neutron beam falling on the spiral phase plate is a statistical mixture of several OAM quantum states. Before applications can be developed, neutrons must be generated that have quantum states with definitive OAM values (eigenstates). In addition, holographic methods have been developed for creating optical[10,11] and electron[12] OAM states, and these are more precise and versatile than the use of spiral phase plates. It will thus be interesting to explore the use of holographic techniques for neutrons too. The potential use of neutron OAM states for quantum-information studies is another exciting prospect.

Finally, Clark and colleagues' study opens up a further avenue for future work: the use of neutron beams with OAM for imaging. Because neutrons are penetrating particles, they could offer practical advantages compared with optical and electron microscopy in deep-imaging studies of materials. One might therefore conclude that OAM-carrying neutron beams may boldly go where no quantum particle has gone before. ■

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50 Years Ago

A Biological Retrospect. By Sir Peter Medawar — The title of my presidential address, as you will have discerned, is "A Biological Retrospect", and on the whole it has not been well received. 'Why a biological *retrospect*?', I have been asked; would it not be more in keeping with the spirit of the occasion if I were to speak of the future of biology rather than of its past? Unfortunately, it is impossible to predict new ideas … and we are caught in a logical paradox the moment we try to do so. For to predict an idea is to have an idea, and if we have an idea it can no longer be the subject of a prediction. Try completing the sentence 'I predict that at the next meeting of the British Association someone will propound the following new theory of the relationships of elementary particles, *namely*…'. If I complete the sentence, the theory will not be new next year; if I fail, then I am not making a prediction.
From *Nature* 25 September 1965

100 Years Ago

We have still … very much to learn about causes in action; and the mystery of the earth, and of our connection with it, grows upon us as we learn. Can we at all realise the greatest change that ever came upon the globe, the moment when living matter appeared upon its surface … And here was living matter, a product of the slime, if you will, but of a slime more glorious than the stars. Was this thing, life, a surface-concentration, a specialisation, of something that had previously permeated all matter, but had remained powerless because it was infinitely diffuse? Here you will perceive that the mere geologist is very much beyond his depth.
From *Nature* 23 September 1915

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EVOLUTIONARY BIOLOGY

Infection elevates diversity

Chromosomal shuffling in parental eggs or sperm can create new characteristics in the next generation. In fruit flies, it seems that mothers with a parasitic infection produce more such recombinant offspring than uninfected mothers.

ANEIL F. AGRAWAL

In most plants and animals, offspring are genetically distinct from their parents. Through the process of recombination, which occurs as sperm and egg cells (gametes) are produced, a parent can mix the two copies of a given chromosome received from its own parents, thus transmitting unique chromosomes to its offspring. Writing in *Science*, Singh *et al.*[1] show that fruit flies produce a higher frequency of offspring with recombinant chromosomes when the mother is infected with a parasite than when it is uninfected. This intriguing observation may be an important piece in the long-standing puzzle of why recombination is so common.

Why should organisms shuffle their genomes through sex and recombination? Natural selection should create an excess of good gene combinations, so 'undoing' the work of past selection by rearranging these genotypes seems counterproductive. One possible explanation is that what constitutes a good combination of alleles (gene variants) changes over time. In that case, undoing the work of past selection is beneficial because selection in the future demands something different. This idea requires that selection on gene combinations changes regularly[2].

Coevolving natural enemies — particularly parasites — might provide just the right type of selection pressures for this scenario. This is the basis for the 'Red Queen' hypothesis, which proposes that sexual reproduction and recombination are favoured because they help hosts to adapt to the ever-shifting selection imposed on their gene combinations by the parasites[3,4]. However, even rapidly evolving parasites do not always induce selection for recombination; there are times in the coevolutionary cycle when hosts are well adapted and non-recombinant offspring will be more resistant to infection than recombinant ones[5,6]. Intuitively, it might seem that the ideal solution is to increase recombination when infected because being infected indicates that your current gene combination is not working.

To test this, Singh *et al.* performed hundreds of test crosses using female *Drosophila melanogaster* fruit flies that carried mutations at each of two genes on one chromosome, but that had normal versions of the genes on their other copy of the chromosome. The presence of either mutation leads to visible physical characteristics that allow determination of whether one or both mutations are present in their offspring — because the genes are in close physical proximity, the normal or mutated versions will be inherited together unless there has been recombination (Fig. 1).

The females were injected with one of two bacterial pathogens (*Serratia marcescens* or *Providencia rettgeri*) or given a sham injection. By examining tens of thousands of the flies' progeny, the authors found that infected mothers produced a higher fraction of recombinant offspring than non-infected mothers. This effect was seen in four fly strains. Infection with a parasitoid wasp (*Leptopilina clavipes*) also induced an increase in recombinant progeny. Unlike the bacterial experiments, in which reproductive adults were infected, the parasitoid wasp infects fruit-fly larvae and the parasites must be killed for the larva to survive to adulthood. Thus, in this situation, the infection is cleared long before meiosis (the cell division necessary to produce gametes and during which recombination occurs).

An increase in the observed frequency of recombinant progeny from infected mothers could be due to an increase in the recombination rate or to transmission distortion (for example, if recombinant chromosomes are more likely than non-recombinant chromosomes to end up in successful gametes). To tease these possibilities apart, Singh *et al.* made use of the fact that exchange of chromosomal material (crossover events) occurs 4–5 days before eggs are laid. In their bacterial-infection experiments, the authors found an increase in recombinant progeny even in the first 4 days after the mothers were infected. This rapid response points to transmission distortion. A remaining challenge will be to understand how this distortion occurs. Are recombinant chromosomes less likely than non-recombinant ones to end up in polar bodies, the small

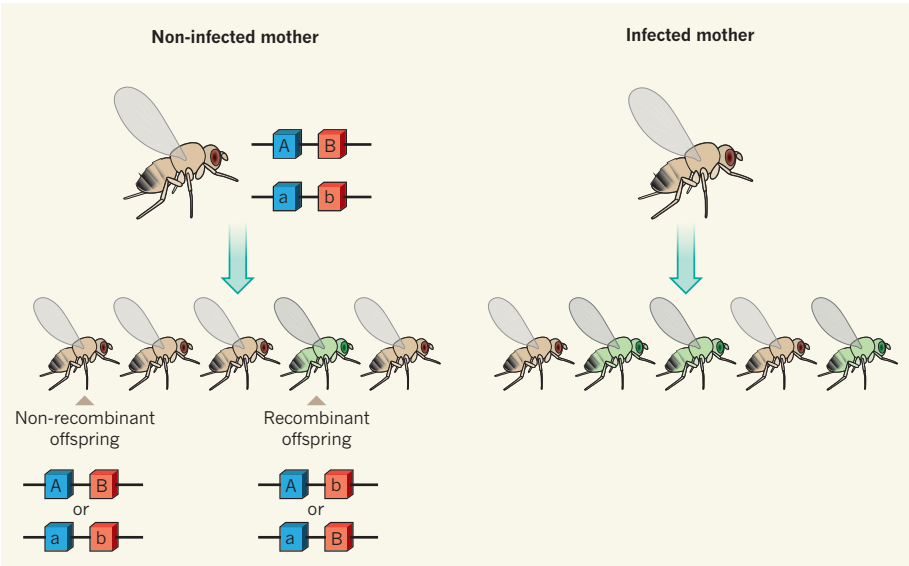

Figure 1 | Frequency of recombinant offspring altered by infection. Diploid organisms, such as fruit flies and humans, have two copies of each chromosome, which can vary in DNA sequence (represented by A versus a and B versus b) in every cell except gametes (sperm and egg cells). Gametes contain only one copy of each chromosome, such that fertilization results in two copies again in the offspring. The sequence in the offspring can be the same as the parental chromosome, or an exchange of genetic material between the two chromosomes during gamete production — recombination — can result in different sequences. Singh *et al.*[1] show that fruit-fly mothers that are infected with parasites produce more recombinant offspring than uninfected mothers.