descendants of this particular event probably suffered no harm, because disrupting one copy of *fukutin* has no adverse effects.

The consequences for modern Japan, however, are quite different. Around 1 in 90 Japanese individuals now carry this same retrotransposon insertion, being descended from the unknown ancestor. The children of two such individuals are at risk of inheriting two disrupted copies, which results in loss of fukutin activity. Although the exact function of fukutin is unknown, it is clearly involved in the attachment of carbohydrate molecules to the α-dystroglycan protein[5,6]. This protein is anchored to the cell surface and, when properly modified by carbohydrates through a process called glycosylation, it forms a crucial link between the intracellular cytoskeleton and the extracellular matrix. In the absence of fukutin, glycosylation is incomplete, and the link is broken. This causes abnormal neuronal migration during development, mental retardation and progressive degeneration of muscle cells.

Because the consequences of Fukuyama-type congenital muscular dystrophy (FCMD) are so devastating, the hunt for the disease gene was naturally undertaken with hopes that identification of the mutation would point the way to developing a treatment. But short of using gene therapy to restore a normal copy of the *fukutin* gene, its discovery[7] had no immediate therapeutic implications. The gene's discoverers continued to pursue the problem, however, and 13 years later they have found a potential opening.

First, they correct a misconception about how the retrotransposon affected *fukutin* expression. Initial studies had indicated that the insertion caused a near-complete absence of *fukutin* messenger RNA, which fitted observations that retrotransposons can silence gene expression. Taniguchi-Ikeda *et al.*[2] re-examine the problem and find that, although part of the transcript is missing, the overall amount of *fukutin* mRNA is not appreciably reduced. However, they notice that splicing of the *fukutin* transcript, a process in which different parts of the primary transcript are joined to create the mature mRNA, is dramatically affected.

The authors found that the effects on fukutin splicing and function in mice were very similar when they artificially inserted the same retrotransposon at the identical location in the mouse *fukutin* gene. They showed that a splice 'donor' site in the final exon (protein-coding region) that had previously been inaccessible was activated and became joined to a newly created splice 'acceptor' site in the retrotransposon sequence, a process known as exon trapping (Fig. 1). Retrotransposon insertions are known to cause exon trapping[8], but this is the first example to show a clear association with disease. Because of this splicing alteration, the carboxy terminus of fukutin is eliminated and replaced instead with amino acids encoded by the retrotransposon sequence. Exactly how this error compromises the glycosylation of α-dystroglycan is unclear, but it may be that the mutant fukutin protein is routed to the wrong cellular compartment[2].

To test whether normal fukutin expression could be restored by correcting the abnormal splicing, the researchers designed 'antisense' oligonucleotides to suppress exon trapping. These molecules are short DNA-like fragments that bind, according to the rules of nucleic-acid hybridization, to the *fukutin* transcript before it is spliced, thereby favourably altering the outcome of the splicing process. This approach had been used previously to suppress or shift splicing sites in other disease states, including other forms of muscular dystrophy[9,10]. In cells derived from patients with FCMD, the antisense oligonucleotides had the intended effect of blocking the deleterious splicing event. As predicted, this led to re-expression of normal fukutin protein and re-establishment of the link between α-dystroglycan and extracellular-matrix proteins. Injecting these oligonucleotides into mice carrying the retrotransposon insertion partially restored normal fukutin protein in muscle tissue, again with improved α-dystroglycan glycosylation.

Could this strategy be adopted to treat children with FCMD? Possibly. But rescuing the associated brain malformation would presumably require treatment *in utero*, a difficult undertaking. The major challenge to the use of antisense oligonucleotides for splice blocking is distributing them into cells in sufficient quantity to influence splicing processes. Although progress has been made in addressing this problem[10], a general solution, applicable for brain and muscle tissue, is not yet available. It is also possible that a similar approach could be applied to other genetic disorders associated with retrotransposon insertion and exon trapping. ■

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QUANTUM MECHANICS

The gentle cooling touch of light

Laser light has been used to cool a nanomechanical resonator to its lowest energy state. The result opens the door to testing the principles of quantum mechanics and to applications in quantum information processing. **See Letter p.89**

FLORIAN MARQUARDT

When you face direct sunlight, besides the brightness and heat that you experience, there is a rather subtle effect. The light produces a force pushing at you — admittedly a tiny one, corresponding to the weight of a few grains of sand. In the past few years, however, researchers have learned how to harness these light forces in the nanoworld and to use them to manipulate the mechanical vibrations of small objects, with remarkable results. On page 89 of this issue, Painter and colleagues (Chan *et al.*[1]) describe how they have exploited laser light to dampen the motion of a nanomechanical resonator. On entering the quantum regime, the vibrational energy of the resonator is no longer continuous. Instead, it is in the form of discrete quanta called phonons. The authors' experiment is the first successful attempt of this type to squeeze essentially all the phonons out of the resonator, leaving the system's vibrations in the lowest possible energy state allowed by quantum mechanics — the ground state. Their results finally pave the way for using light to realize many quantum-physical phenomena in such structures.

The force exerted by light, called the radiation pressure force, was first demonstrated a little more than 100 years ago. Radiation forces have been remarkably successful in manipulating the motion of atoms (for example, in laser-cooling them or trapping them within optical lattices produced by the interference of laser beams). They have also been

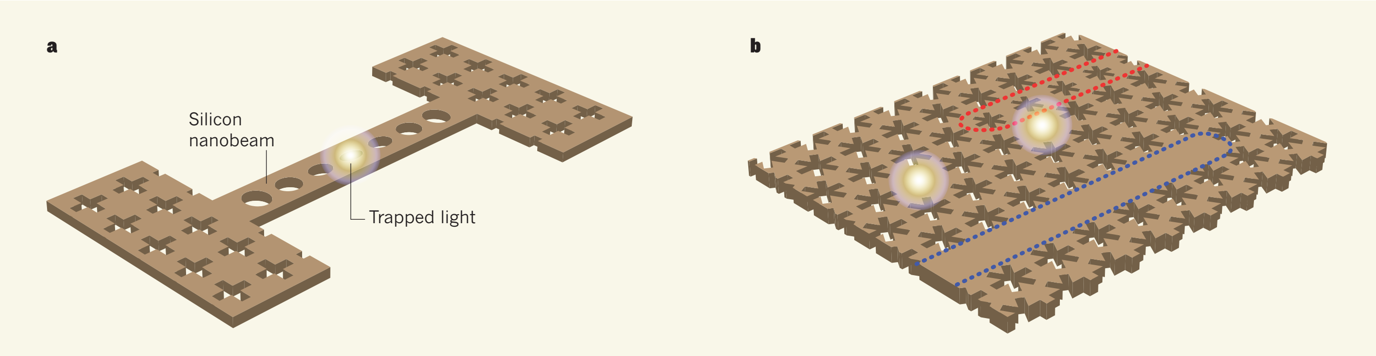

Figure 1 | Coupling light and mechanical motion. **a**, Chan *et al.*[1] patterned a free-standing silicon nanobeam with holes to trap incoming laser light in its central region. This design allowed them to couple the light to the nanobeam's mechanical vibrations (not shown) and bring a particular vibrational standing wave to the quantum-mechanical ground state. **b**, The team already has designs[10] for two-dimensional photonic-crystal structures — similar to the one shown here — that might form the basis for optomechanical circuits in which light and mechanical motion could be coupled to one another and to optical (blue) and acoustic (red) waveguides. The devices' mechanical and optical functionalities are purely the result of carefully engineering the shapes of the holes cut into the structures.

used to manipulate larger objects such as glass beads, whose motion can be controlled through 'optical tweezers'.

Over the past few years, similar ideas have been applied to control the vibrational motion of nanofabricated structures. A typical set-up involves using a laser to illuminate an optical cavity — an arrangement of two reflective mirrors that allows light to bounce back and forth between them — in which the circulating radiation exerts a force on a mechanical element, such as a vibrating cantilever carrying one of the cavity's mirrors. A large variety of set-ups is being investigated in this rapidly growing field of cavity optomechanics[2]. They involve, for example, not only membranes, microtoroids and nanoscale slabs termed nanobeams, but also vibrating structures coupled to superconducting electrical devices that are driven by microwave radiation instead of by laser light. The field is motivated both by fundamental questions about quantum mechanics and by more applied aspects, such as the ultrasensitive detection of small displacements or forces and possible uses in quantum information processing.

To enter the quantum regime, mechanical vibrations have to be as cold as possible, which can be achieved by laser cooling. The basic idea is simple enough: send in laser light consisting of photons that do not have quite enough energy to enter the optical cavity, except when they grab an extra quantum of energy from the mechanical vibrations thereby cooling them. The essence of radiation-induced damping of mechanical vibrations was demonstrated[3] in 1970 in a macroscopic set-up. In 2004, this principle was first applied to cooling a micromechanical resonator using a force created by the thermal effects of light[4], and in 2006 three groups[5–7] showed the kind of radiation-pressure laser cooling that has now[1] finally led to cooling a nanomechanical resonator to the quantum ground state. Nevertheless, it proved hard to find a system that combined a sufficiently strong light–mechanics coupling with a weak enough coupling to the thermal environment, and to pre-cool the system to low temperatures using standard methods.

Chan *et al.*[1] have now overcome these challenges. Their experiment is based on a design introduced two years ago by Painter and colleagues[8]. A silicon nanobeam that has a suitable arrangement of holes (forming a photonic crystal) traps incoming laser light in its central area, in a region not much larger than the wavelength of light, essentially forming an optical cavity (Fig. 1). The beam is free standing, so it can vibrate, and there are standing waves of mechanical vibrations localized at the area where the light is trapped. These are of a high (gigahertz) frequency, making it easier to cool them, and the strong overlap between the tightly localized light field and the mechanical vibrations yields an exceptionally large optomechanical coupling.

In addition, the team exploited the design flexibility of this 'optomechanical crystal' device to engineer a structure in which the damping of vibrational motion is strongly reduced. The combination of all these factors led to successful laser cooling to the ground state: starting with 100 phonons at a temperature of about 20 kelvin, the team[1] was able to reduce the energy of a particular vibrational standing wave to less than one phonon on average. Together with a recent analogous experiment[9] performed in the microwave domain, Chan and colleagues' study[1] opens the door to exploring the quantum regime of cavity optomechanics.

With the latest advance, it will now become possible to produce non-classical states of light and mechanical motion. One example would be the generation and detection of quantum entanglement in the system — correlations between the light and the mechanical motion that are stronger than anything possible in classical physics. Ultimately, light could even be used to create entanglement between mechanical objects separated by a distance. Another enticing prospect is to engineer optomechanical arrays and circuits that couple many optical and mechanical oscillations. Such designs could integrate several functionalities, for applications such as sensing and signal processing, or could be used to study the collective dynamics of photons and phonons on a chip. If the coupling between a single photon and a single phonon could be increased 500-fold from the value achieved here, thus making it larger than the photon decay rate in the current set-up[1], then interesting nonlinear quantum effects could be observed.

Finally, researchers in quantum information science are delighted by the prospect of making a device, possibly based on the Painter team's design[10], that converts single phonons to photons. Combining such a device with the already demonstrated[11] strong coherent coupling between a nanomechanical resonator and a superconducting two-state quantum system, or qubit, it might be possible to realize an interface between such solid-state qubits and photons, which is much needed for quantum communication applications. ■

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