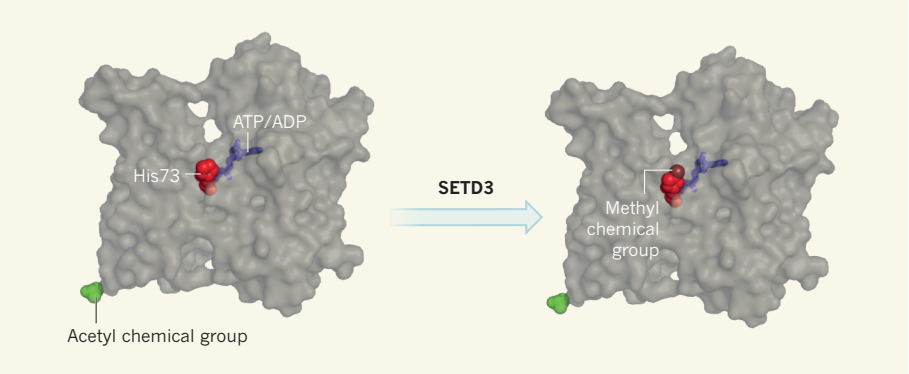

KONSTATIN KOGAN

Figure 1 | Methylation of actin by the SETD3 protein. Wilkinson *et al.*[2] show that SETD3 catalyses the addition of a methyl chemical group (methylation) to a histidine amino-acid residue (His73) of the protein actin, and that this modification fine-tunes the protein's function. His73 is close to a site to which either an ATP or an ADP nucleotide binds. The switch between ATP and ADP is essential to allow actin filaments to produce force in cells. Other evolutionarily conserved post-translational modifications of actin, including the addition of an acetyl chemical group (acetylation) to its amino-terminal region, are distant from the nucleotide-binding pocket of actin.

in mammals, SETD3 is the only enzyme that catalyses the His73 methylation of actin, and that actin is the only substrate of SETD3. They also show that SETD3 and His73 methylation of actin are present in a wide range of organisms, including plants and animals, but that SETD3 is not present in budding yeast, which also lacks His73-methylated actin.

Why does SETD3 methylate actin, but not other proteins? To answer this question, Wilkinson *et al.* determined the atomic structure of SETD3 in complex with a short chain of amino acids (a peptide) that has the same amino-acid sequence as the region of actin around His73. They found that this peptide occupies an extended groove in the domain of SETD3 that is responsible for the enzyme's methyltransferase activity. The interface between SETD3 and the actin peptide has many specific interactions, which explain why SETD3 binds to and methylates only actin.

To examine the biological functions of this post-translational modification, Wilkinson *et al.* generated 'knockout' mice and cell lines in which the gene encoding SETD3 was inactive. They observed that actin is no longer methylated in these models. Surprisingly, the mice lacking SETD3 seemed to be healthy, which demonstrates that methylation of actin at His73 is not essential in mammals. However, female mice lacking SETD3 took longer to give birth than did mice in which this protein was present. The delay resulted from defective contraction of certain muscles of the uterus during labour. Moreover, the migration of SETD3-knockout cells in culture was slower than that of wild-type cells. Finally, non-methylated actin purified from the SETD3-knockout cells polymerized slightly more slowly than did methylated actin, and had a faster rate of exchange of nucleotides on single actin molecules than did actin purified from wild-type cells.

These experiments provide evidence that, despite being evolutionarily conserved across a broad group of organisms, methylation at His73 is not essential for the normal functioning of actin. Instead, this modification seems to fine-tune the protein's biochemical properties and cellular roles.

Future studies should investigate the SETD3-knockout mice in more detail for possible additional differences from wild-type mice, and should examine the effects of SETD3 deletion in other model organisms. Also, the effects of His73 methylation on actin biochemistry should be studied more precisely. Previously, analysing these effects was possible only by mutating the His73 residue in actin or by producing human actin in yeast, in which this protein cannot be methylated[9,10]. The new findings will enable careful side-by-side comparison of wild-type actin and actin that lacks methylation only at His73.

Because His73 is close to the nucleotide-binding site of actin, it will be especially interesting to study how this modification affects the functions of proteins that catalyse nucleotide exchange on actin[11] and that rely on ATP hydrolysis and subsequent release of free phosphate for their interactions with actin filaments[12]. ■

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BIOTECHNOLOGY

Implant aids responsive bladder control

Implants that electrically stimulate nerves continuously to treat disease can cause off-target effects and pain. An implant that uses light to modulate the activity of genetically modified nerve cells might offer a solution. SEE LETTER P.361

ELLEN T. ROCHE

Advances in bioelectronics have enabled progress[1] in the use of implanted electronic devices for treating disease. In the clinic, such approaches to modulating nerve cells that control bladder function[2] can treat a condition called overactive bladder, which is characterized by a frequent urgent need to urinate, sometimes with associated incontinence, and an abnormally high number of bladder-emptying episodes. The conventional approach taken for such nerve modulation is to apply continuous electrical stimulation; this does not affect only the relevant nerve cells, however, and can lead to pain and off-target effects[3]. Mickle *et al.*[4] describe on page 361 a potential way of tackling this problem — a miniature implanted device that can sense and control bladder function in rats.

Rather than modulating nerve activity through the direct use of electrical stimuli, the authors harnessed an established technique called optogenetics, in which nerve cells in the bladder were genetically modified to express a light-sensitive receptor protein that can inhibit nerve-cell activation. Mickle and colleagues implanted a stretchable, high-precision strain sensor around each animal's bladder that measured changes in bladder circumference over time. The bladder sensor was connected

to light-emitting diodes (LEDs). These components were connected by wires to a flexible base-station device implanted in the abdomen. The base station was powered wirelessly by interactions with an element incorporated below the housing cage (Fig. 1).

The bladder-stretch sensor communicated data to the base station, which then wirelessly transmitted this information to an external device that recorded and monitored bladder function. If the external device detected signs of abnormal bladder function — for example, unnecessarily frequent bladder emptying — it transmitted a signal wirelessly to the base station. This made the LEDs turn on, causing light-mediated inhibition of sensory neurons in the bladder that thereby affected the frequency of bladder emptying. This type of arrangement is called a closed-loop system, in which the output of the system — in this case, bladder size changes — is monitored and feeds back into the system as an input signal. This is advantageous in this context because it triggers the modulation of nerve-cell activity only when needed, providing a targeted, real-time control system.

The authors tested how effective their system was for managing the bladder dysfunction that arises when rats are injected with the drug cyclophosphamide. This causes an inflammatory response and an increase in the number of episodes of bladder emptying compared with that in animals that do not receive cyclophosphamide. The authors' system detected dysfunctional patterns of bladder emptying and consequently inhibited the organ's sensory nerves and restored a normal pattern of urination frequency.

Mickle and colleagues' device is possible only because of many recently developed relevant tools. The authors needed implantable flexible sensors and stretchable electronics that can detect organ-dimension changes in a way that does not affect organ function[5–8]. Developments in the field of optogenetics, wireless data and energy transfer also provided crucial technologies needed for the system to function.

The animal model of overactive bladder function that the authors chose for their system reveals the sophisticated capabilities of this technology. Whether this versatile platform could be adapted to treat other diseases should be explored. Mickle and colleagues' work might have major implications for efforts to alleviate organ dysfunction and to modulate pain. However, it was not possible to determine whether the pain caused by bladder infection and the inflammation that can be associated with bladder dysfunction can be lessened by using the authors' approach, and the effects of inhibition of sensory nerves using this method should be a topic for further investigation.

It was previously shown[9] that, for a surgically removed rabbit heart being kept functional in the laboratory, a stretchable, sleeve-like electronic device surrounding the heart can detect data such as temperature, pH and mechanical strain. If such a heart-monitoring device could be modified to incorporate the closed-loop control system developed by Mickle and colleagues, it might provide real-time feedback that could be used to modulate the activity of the implanted pumps or sleeves (called ventricular assist devices) that aid people who have a weakened heart[10,11]. Or, one day, a closed-loop system might be used to detect stretching of the stomach and relay this information to drive a feeling of fullness, as a way of managing obesity. Could this closed-loop system have the potential to be adapted into a medical device that enables normal bowel emptying for people with faecal incontinence caused by nerve damage?

The approach developed by Mickle and colleagues has several key features. Using an optical system to modulate nerve-cell function provides greater stability and temporal precision than does electrical stimulation. Flexible electronics that conform to an organ surface offer a stable interface in which the electronic device matches the mechanical properties of the associated tissue. If it were possible to use input from physical cues such as changes in organ geometry, blood-flow dynamics or temperature in a closed-loop therapeutic device, this would open up a new way of thinking about how to harness biological sensing for clinical purposes. In contrast to current sensor techniques, which use cues such as chemical signals in blood-glucose monitors or electrical signals in heart pacemakers, focusing instead on easily measured physical cues might substantially increase the number of ways of assessing the function of an organ.

This study provides a groundbreaking demonstration of how a fully closed-loop system can sense and control organ function, but there are some drawbacks. The wireless-powering mechanism requires a device that is placed underneath the animal's cage, so alternative strategies would be needed to provide a wireless energy source for clinical use. Another disadvantage is that the optogenetics approach relies on the genetic modification of cells. In this case, a virus was used to introduce the engineered gene into bladder cells by injection into the bladder wall after a surgical incision through skin and muscle to expose the bladder. Moreover, this step was carried out some time before device implantation, and a requirement for repeated bouts of surgery could generate a barrier to the clinical implementation of this approach. Furthermore, if part of the system failed and needed to be replaced, additional invasive surgical procedures would be needed to remedy the problem.

The body's long-term response to the presence of a stretchable sensor around the bladder is unknown. It is also of concern that associated tissue damage might occur, such as the formation of excess fibrous connective tissue (fibrosis), or whether adhesions to surrounding tissue might arise that could limit implant function and have adverse effects on organ function.

Mickle and colleagues have taken a major step forward for this field by developing a therapeutic system that enables specific and stable stimulation of the nervous system. If

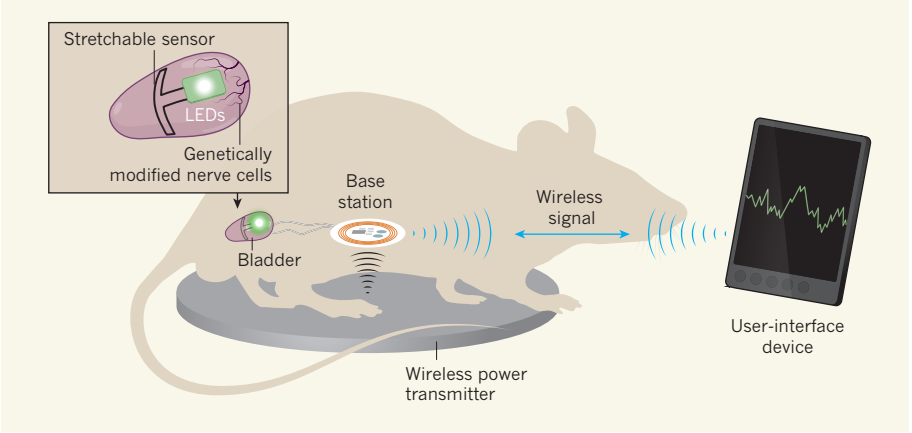

Figure 1 | An engineered system that alleviates bladder dysfunction. Mickle *et al.*[4] have developed an approach that uses genetic engineering and an implanted device to generate a self-adjusting system (called a closed-loop system) that regulates nerve-cell activity to treat organ dysfunction in rats. The authors used animals that had been genetically engineered to express a light-sensitive protein in sensory nerve cells in their bladder. A stretchable sensor implanted in the bladder monitored the organ's circumference, and it was attached to light-emitting diodes (LEDs). These bladder components were connected by wires to an implanted base-station electronic device in the abdomen that was powered wirelessly by a transmitter in the animal's cage. The base station received information from the bladder's stretch sensor and transmitted this wirelessly to an external user-interface device that tracked the bladder data. If the data indicated abnormally frequent bladder emptying, which happened when animals received the molecule cyclophosphamide (not shown), the external device transmitted a wireless signal back to the base station that caused the LEDs to turn on. Their illumination inhibited the genetically engineered nerve cells and consequently prevented an abnormally high frequency of urination.

optogenetics approaches are approved for specific clinical applications, this type of closed-loop system might be poised to have a key role in driving a transformative shift towards the use of such strategies to treat human disease. ■

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ASTROPHYSICS

Heart of a stellar explosion revealed

During the deaths of some massive stars, a narrow beam called a jet is launched through the stellar envelope, leaving an imprint that is difficult to detect. Such an imprint has now been seen in unprecedented detail. SEE LETTER P.324

EHUD NAKAR

The death of a massive star is a spectacular event. When the star has consumed all of its nuclear fuel, its core collapses. This leads to a strong blast wave that ejects the stellar envelope at a velocity of about 1–3% of the speed of light, producing a supernova explosion[1]. In rare cases, the collapsing core also launches an energetic beam of matter and radiation, known as a jet, through the stellar envelope at almost the speed of light[2]. The jet emerges from the stellar surface and generates a bright burst of γ-rays, which can be seen only when the jet points directly towards Earth. On page 324, Izzo *et al.*[3] report spectroscopic observations of a supernova associated with a γ-ray burst, improving our understanding of the interplay between the jet and the exploding stellar envelope.

Theory predicts that, as a jet pushes its way through a stellar envelope, it heats the gas that surrounds its path, producing a highly pressurized, hot bubble known as a cocoon[4–6] (Fig. 1a). As the jet breaks out of the star, so does the cocoon[7] (Fig. 1b; see also the movies at go.nature.com/2sdoeao). The cocoon carries information about the interaction between the jet and the envelope and opens a window on the inner workings of the explosion.

The predicted signature of the cocoon initially includes a relatively faint flare of γ-rays that is emitted when the cocoon breaks out of the stellar envelope[8–10]. This is followed by a fading signal that is seen first in X-rays and later in ultraviolet and optical light[11]. In addition, the cocoon spreads sideways, engulfing the expanding envelope so that the supernova light must pass through the cocoon material on its way to Earth. During the first few days after the explosion, this passage leaves an imprint of broad absorption features on the spectrum of light from the supernova[12]. Later, as the cocoon expands, it becomes fully transparent, and the absorption features disappear.

For decades, astronomers have been observing the emissions from ejected envelopes and from jets — the supernovae and the γ-ray bursts, respectively. However, although cocoons are predicted to transport as much energy as the other two components[11], identifying their observational signatures turned out to be extremely difficult. When a jet is pointing towards Earth, the γ-ray burst and the afterglow of the burst outshine the cocoon emission, as well as the supernova light, for several days. And when a jet is pointing away from Earth, the supernova is usually detected too late, after the absorption signal has disappeared. Izzo and colleagues present observations of an event in which a γ-ray burst is seen, but the afterglow of the burst is faint enough to

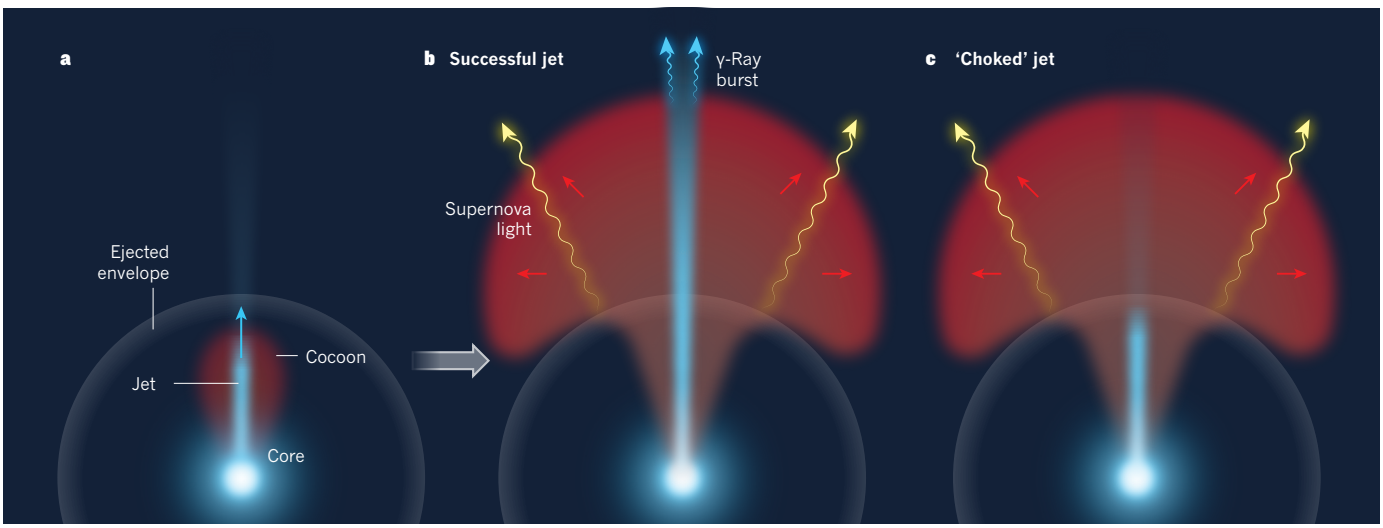

Figure 1 | Jets and cocoons in supernova explosions. **a**, During the death of a massive star, the stellar envelope is ejected to produce a supernova. In rare cases, the core of the star launches (blue arrow) a narrow beam of matter and radiation called a jet through the envelope, generating a hot bubble known as a cocoon. Izzo *et al.*[3] report observations of such a cocoon in a particular supernova. **b**, If the jet successfully breaks out of the stellar envelope, it produces a bright burst of γ-rays. The cocoon also breaks out, and spreads sideways (red arrows) to engulf the star. Supernova light from the envelope is partially absorbed as it passes through the cocoon on its way to Earth. **c**, In other supernovae, jets can be 'choked' — they lose all of their energy while still inside the envelope. However, the cocoon can still break out and form an outflow similar to that of the cocoon of a successful jet.