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BIOPHYSICS

Fashionable cells

Chun Y. Seow

How can cells deform yet maintain optimal function? Probing the similarities in the properties of a cell's network of structural filaments, and those of soft glassy materials, may help in tackling this question.

Most of the cells that make up our body are supported by a cytoskeleton, an internal network of protein filaments. This network does not merely act as a scaffold that defines cell shape and organizes intracellular organelles, but also allows the cell to be malleable and motile, and adapt to strains imposed internally and externally. As they report in *Nature Materials*, Bursac *et al.*[1] have combined observations of the cytoskeleton in action with some principles derived from condensed-matter physics to offer a fresh perspective on cytoskeletal dynamics.

The need for a cell to deform while maintaining function is most obvious in the smooth muscle cell, which is embedded in the wall of hollow organs such as the urinary bladder, lungs (airways) and uterus. These organs undergo large changes in volume, implying substantial changes in cell length. Surprisingly, these drastic alterations in cell dimensions do not appear to affect cell function. The concept of plastic length adaptation was first developed for the smooth muscle of airways[2,3], to explain how muscle can generate maximal force over a large range of lengths. It then soon became evident that the network of contractile and cytoskeletal filaments in smooth muscle is in a constant state of rearrangement, driven by the strains applied to the network.

Like the cytoskeleton, soft glassy materials such as pastes, colloids and foams can accommodate drastic changes of shape. Such changes occur when a cold glass, a rigid solid, is heated to a temperature at which it starts to behave as a malleable fluid. As they go about their daily business of adhering and spreading, crawling and invading, or contracting and relaxing, the cells of our body seem to orchestrate their mechanical properties in much the same way as happens in soft glasses around the glass transition temperature (which marks the crossover point between solid and fluid characteristics). But instead of changing temperature, the cell modulates something else, although with much the same effect — an 'effective temperature'[4].

Bursac *et al.*[1] reveal further details of the behaviour of the cytoskeletal and contractile filament network of smooth muscle cells, and its striking resemblance to how soft glassy materials respond to stress and strain. Their experiments involved attaching a microbead to the cytoskeleton of cultured smooth muscle cells from human airways, then following its spontaneous movements. They find that the microbead's movement reflects motion associated with molecular-scale rearrangements of the filament network. Most of the time nothing of great interest happens; motions are sub-diffusive, suggesting that proteins are trapped in a cage formed by weakly interacting structural proteins in a 'crowded', out-of-equilibrium microenvironment. But these sub-diffusive motions are punctuated by intermittent events thought to reflect 'hops' of the structural proteins out of one cage and into another, driven by the tendency of the discrete constituents of the crowded environment to settle slowly into a slightly more stable configuration.

An analogous hopping phenomenon has been observed in colloidal glasses[5], and the slow settling process is known as ageing. Ageing can be reversed by a process called rejuvenation, when a soft glass is subjected to a large shear that breaks up constraints and restores the previous state of disequilibrium. Bursac

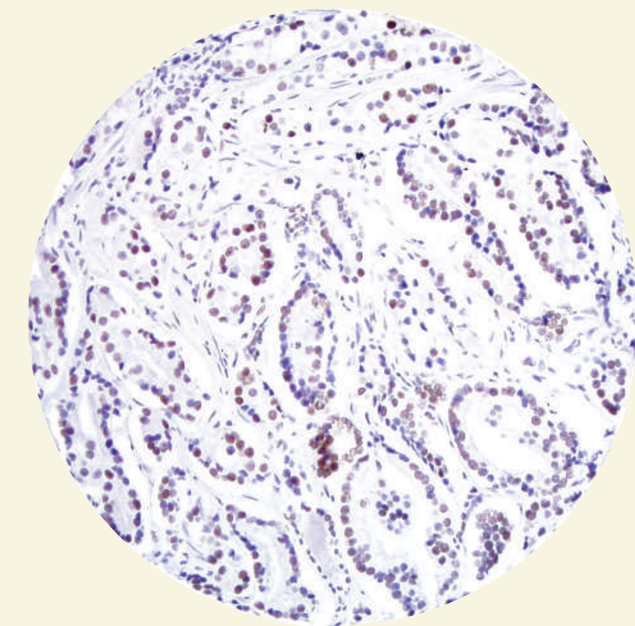
CANCER

A changing global view

Global gene-expression profiles have emerged as a way to divide tumours that look similar into subgroups with distinct prognoses. But they can be technically demanding and difficult to implement as a routine clinical assay. Siavash Kurdistani and colleagues show elsewhere in this issue (*Nature* **435,** 1262–1266; 2005) that taking a different global view — of histone modification — can provide a similar indicator, for prostate cancer at least, that may translate easily to the clinic.

Histone proteins, around which DNA is wrapped to pack it into the nucleus, can be chemically modified in several places by the addition of acetyl or methyl groups. These modifications are reversible and can affect the expression of the associated genes. Cancer cells are known to have unusual patterns of histone modification, but so far work has focused on individual genes and their contribution to cancer development and progression.

In contrast, Kurdistani and colleagues looked at global levels of the acetylation or methylation of five different residues in histones H3 and H4 in prostate tumour samples. They used antibodies that were specific for each modification to highlight any differences; for example, the photo here shows a section of low-grade prostate cancer tissue (Gleason score 6) stained with an antibody against dimethylated arginine 3 of histone H4.



DAVID SELIGSON

The authors found, from two independent sets of prostate cancer samples, that histone modification patterns can forecast the risk that a low-grade tumour will recur after surgical removal. How the observed global changes in histone modifications relate to the regulation of genes relevant to prostate cancer development is not known. However, using immunochemistry to detect bulk histone modifications in cancer samples is relatively easy, so these findings could be translated directly into prognostic markers for clinical use.

Barbara Marte

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et al.[1] show that the cytoskeleton of smooth muscle cells can age and rejuvenate in a similar manner.

So insights gained from advances in understanding inert glassy materials can be applied to the cytoskeleton. But there are of course dissimilarities. As Bursac *et al.* point out, interactions of structural proteins depend on the energy supply from within the cell in the form of ATP hydrolysis. The energy supply and protein–protein interactions that drive the cytoskeletal reorganization are precisely regulated in cells[6]; similar active regulation does not occur in the case of glass deformation driven by strain and thermal energy.

The notion that the cytoskeleton of a smooth muscle cell is malleable[1,4], and that the malleability is probably precisely regulated[7], is important for our understanding of how smooth muscle and other cell types work. Although a cell needs to be malleable to accommodate large changes in geometry, it also needs to be rigid to generate or transmit force. Some mechanisms underlying the ability of smooth muscle to plastically reorganize its contractile[2,7] and cytoskeletal[3,8] filaments have been proposed, but many aspects of the cell's adaptive behaviour remain unknown.

The effects of cell malleability on organ function is another area that requires investigation. It is easy to appreciate why the smooth muscle cell needs to be malleable in hollow organs that undergo large changes in volume, but for other cell types that need is less obvious. It is likely, however, that the ability of the cell to rearrange the molecules of its internal skeleton is essential in such events as vessel narrowing, wound repair and cell migration. Abnormality in the regulation of cell malleability may therefore underlie conditions such as cell invasion in cancer, and the excessive narrowing of airways and blood vessels seen, respectively, in asthma and hypertension. The report of Bursac *et al.*[1] gives us a different way to think about how this basic rearrangement process might work. ■

Chun Y. Seow is in the Department of Pathology and Laboratory Medicine, James Hogg iCAPTURE Centre, University of British Columbia, Vancouver, British Columbia V6Z 1Y6, Canada.
e-mail: cseow@mrl.ubc.ca

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IMAGING TECHNIQUES

Particular magnetic insights

Andreas Trabesinger

Over the past 30 years magnetic resonance imaging has been refined into a widely used technique. A method known as magnetic particle imaging has now been devised which offers an inner view from a different angle.

It is fairly easy to record electrical signals from the human body, as with an electrocardiogram. The extraction of magnetic signals is a more subtle business, typically involving strong magnets and exquisitely sensitive detectors. In a magnetic resonance imaging (MRI) experiment, this effort is well rewarded, as the technique reveals fine details of a subject's inner life[1]. The approach can be pushed further by introducing strongly magnetic particles into the body which selectively perturb the weak natural MRI signal and increase the image contrast[2]. Direct imaging of these particles, however, has seemed less feasible — hence the appeal of the report by Gleich and Weizenecker[3] (page 1214 of this issue), which lays out a way to do just that.

Contrast agents that incorporate magnetic particles are routinely used in clinical MRI examinations. These biocompatible 'spies', typically based on rare-earth elements or iron oxides, can highlight specific anatomical structures, such as blood vessels or (under certain circumstances) tumours. Furthermore, they can serve as markers for processes at the molecular level[4].

The valuable information contained in the spatial distribution of the magnetic contrast agent is recorded indirectly. In these contrast-enhanced MRI studies, the strong magnetization of the magnetic particles is used to alter the signal of the (orders of magnitude) weaker intrinsic nuclear magnetization of the body. Looking directly at the contrast agent could potentially translate its stronger magnetization into a stronger signal — or, alternatively, reduce the contrast agent required to minute amounts. However, resonance methods such as those used for MRI are often unsuitable for imaging magnetic particles, and 'inversion methods' that detect the magnetic field outside the object do not provide high spatial resolution.

Gleich and Weizenecker[3] present an approach — magnetic particle imaging (MPI) — for capturing and localizing the signal of magnetic particles inside the body. In their initial demonstration, they filled holes in a plastic plate with a commercial contrast agent (nanometre-sized particles of iron oxide, coated with dextran). When a magnetic field is applied to this assembly, the contrast agent becomes magnetized. The response to a changing magnetic field is more or less immediate, until the magnetization reaches saturation above a certain field. A further increase in field will leave the magnetization unaffected.

Now imagine that the particles in a magnetic field are further irradiated by a weak radio-frequency field (Fig. 1b–d). Saturated magnetic particles will stay in this state (Fig. 1b, d), whereas unsaturated ones will readily reply with an oscillating magnetization (Fig. 1c). As the response is nonlinear, it will contain frequencies that are different from the driving frequency of the radio-frequency field.

These signals announce the presence of magnetic particles in the body, but not their location. To add this crucial component,

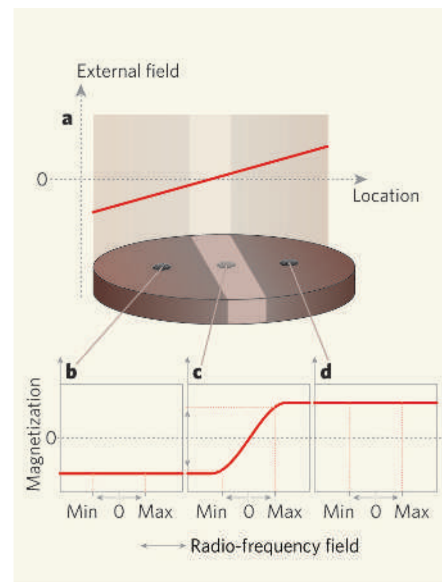

Figure 1 | Principle of the imaging technique devised by Gleich and Weizenecker[3]. a, The object to be imaged is immersed in an external field whose strength varies with location. In most regions the magnetization of a magnetic particle sitting inside the object is saturated (dark areas). **b,d,** An additional weak radio-frequency field — oscillating between a minimum and a maximum value — cannot change this state. **c,** However, in regions where the external field has a value close to zero, the additional field is able to alter the magnetization, which will start to oscillate and therefore induce a signal in a detection circuit. This signal can be unambiguously assigned to the narrow field-free region. By systematically varying the position of the field-free area in the object, a map can be created that gives the spatial distribution of the magnetic particles.

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