FORUM Biological physics

Liquid crystals in living tissue

Evidence has been found that a biological tissue might behave like a liquid crystal. Even more remarkably, topological defects in this liquid-crystal system seem to influence cell behaviour. A materials physicist and a biologist discuss what the findings mean for researchers in their fields. SEE LETTER P.212

THE PAPER IN BRIEF

- Epithelial tissues line the cavities and surfaces of organs throughout the body.
- Such tissues remove unnecessary or disease-causing cells through an extrusion process.
- Saw *et al.*[1] (page 212) have modelled the epithelium as a type of 'active' liquid crystal, in which the movement of cells generates topological defects.
- They report a universal correlation between extrusion sites and positions of defects in the liquid crystal.
- The work opens up opportunities for further studies into the feedback between the cellular arrangement within tissues and key biological processes.

Active matter in biology

LINDA S. HIRST

Saw and colleagues' study demonstrates how the physics of soft matter can contribute to a deeper understanding of biological systems. The authors show that compressive stresses induced by orientational ordering and defects in the epithelium provide a physical trigger for cell death. What makes this paper particularly exciting is its resonance with an emerging field in condensed-matter physics: active matter.

Physicists often seek to apply the thermodynamics and mechanics of soft materials to biological systems, but this approach has some important limitations. Living systems are typically not in equilibrium: cellular and subcellular systems are constantly changing their structure in response to stimuli, consuming energy stored in ATP molecules. One of the most exciting developments in soft condensed-matter physics over the past few years has therefore been the rapid expansion of research into active matter, which — unlike classical solids and liquids — is not in equilibrium.

There are many examples of active matter in nature, ranging from flocks of birds and insect swarms[2] to cells[3] and combinations of biopolymers and molecular motors[4]. The unifying theme is that collections of subunits (birds, cells, biopolymers, and so on) take in energy locally, and then translate that energy into movement that can, in turn, produce large-scale dynamic motion[5]. Internal motion throughout an active material can also result in the formation of emergent dynamic structures, including topological defects at which local order breaks down.

So where does Saw and colleagues' work fit into this? Epithelial cells are somewhat elongated and closely packed, which means that they can spontaneously align in a similar way to the molecules in nematic liquid crystals — fluids that exhibit orientational molecular order. Saw *et al.* demonstrate that epithelial cells seem to behave like an active nematic that contains moving, comet-shaped topological defects (Fig. 1).

Remarkably, the authors report that this behaviour provides a mechanism for cell extrusion. To confirm this, they performed experiments in which geometrical constraints produce sheets of epithelial cells that have well-defined defect configurations. When they induced defect formation at specific locations, they observed that cells are preferentially extruded from those sites. In a paper online in *Nature*, Kawaguchi *et al.*[6] report evidence of similar active nematic behaviour in neural progenitor cells, and show that accumulation and expulsion of these cells also occur at topological defect sites.

So why is cell extrusion triggered at defect points in epithelial-cell layers? Using a technique called traction force microscopy[7], Saw *et al.* detected substantial compressive stresses around particular defect types (known as +1/2 defects) at which cells were most likely to be extruded. They also observed that cytoplasmic levels of a stress-triggered protein (YAP) were increased at the +1/2-defect sites, compared with levels in cells at other sites, suggesting a stress-induced mechanism. Levels of caspase-3 — an enzyme associated with apoptotic cell death — are also increased at the defects.

Saw and co-workers convincingly argue that the active, nematic nature of the epithelium provides a physical mechanism for regulating cell extrusion — a remarkable and beautiful example of the role of soft-matter physics in biology. It is also one of relatively few experimental examples in which collective dynamics give rise to theoretically predicted behaviour. The stage is now set for further discoveries related to active materials in biology, a field of physics that can closely model living systems.

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Biological matters arising

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Epithelia must be continuously renewed to carry out their barrier function. Previous work[8,9] established that these tissues have a preferred cell density that is maintained through a balance between cell division and removal (which occurs through extrusion). But why some cells rather than others are targeted for removal was mysterious. Saw and colleagues' explanation adds to a growing body of evidence of feedback between physical effects, mechanical forces and biological behaviour.

The constituent molecules of nematic liquid crystals are elongated and show orientational order. Similarly, migrating cells generally possess a long axis, and the direction of movement of adjacent cells is closely correlated. Saw *et al.* show that defects similar to those of nematic liquid crystals occur in epithelia, that the stress distributions around the defects are similar to those in nematics, and that the location of

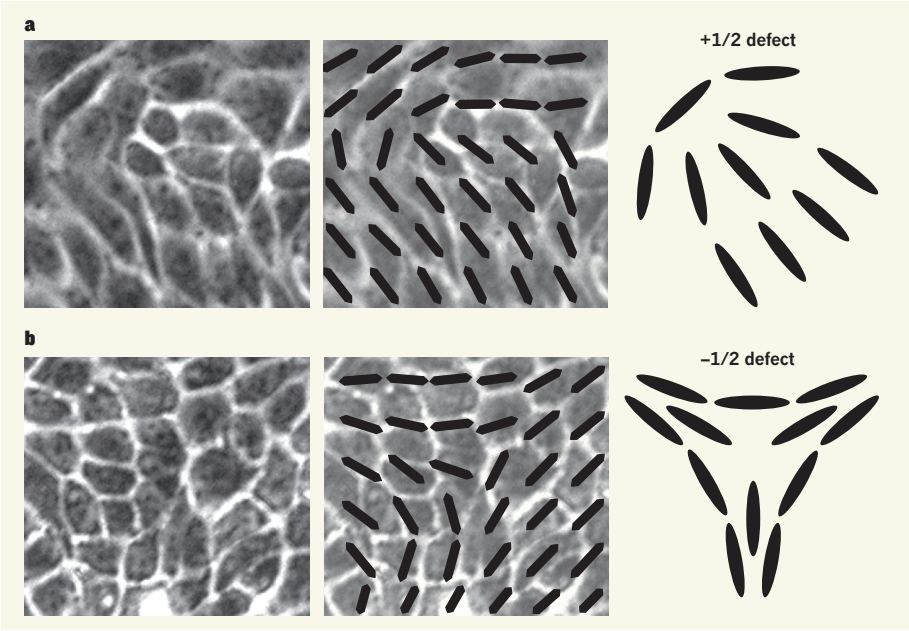

Figure 1 | Defects in systems of epithelial cells. Saw *et al.*[1] report that epithelial cells align in a manner similar to the molecules in 'nematic' liquid crystals, and that certain defects in the liquid-crystal structure correlate with locations at which cells are extruded from the cell system. **a**, The micrograph on the left shows part of a layer of epithelial cells studied by the authors. In the centre panel, the local average orientations of the cells are indicated by black lines. These correspond to the orientations associated with a defect known as a +1/2 defect (right). **b**, In this case, the cell orientations correspond to a −1/2 defect. Saw *et al.*[1] find that cell extrusion occurs predominantly at +1/2 defects.

extrusions correlates closely with +1/2 defects. Epithelia thus seem to behave much like liquid crystals.

What molecular mechanisms underlie the nematic-like behaviours of cells? Intercellular adhesion has a crucial role in coordinating the collective migration of cells, thereby ensuring high orientational order — a fundamental property of nematics. Consistent with this, Saw and co-workers observed that reducing intercellular adhesion between epithelial cells reduces orientational order and leads to an increase in defects and extrusions.

It has been shown previously that cell extrusions are often the result of signalling events that take place over several hours[10]. An open question therefore arising from the current work is how long cells must reside close to a defect to trigger extrusion. Furthermore, the authors' observation that extrusions commonly occur in the vicinity of +1/2 defects but less so near other types of defect (−1/2 defects) is puzzling. A comparison of the different defect types will probably aid our understanding of the link between tissue topology, mechanical stimuli and cell fate.

More generally, this discovery reflects a continuing trend of transposing theories developed for non-living systems to biological materials. It is unclear at present whether liquid crystals and epithelia are truly close analogues, or whether cell-specific adjustments to the theory of nematics will be necessary to fully explain cell dynamics in liquid-crystal-like tissues. Nevertheless, the concept of cellular nematics offers an exciting theoretical framework that provides a link between organization at the tissue scale and the behaviour of single cells. As such, it might be useful in many areas of biology.

For example, extrusions are commonplace during embryonic development. Is the spatial location of these extrusions controlled solely by genetics, or does local tissue organization also participate? The new findings are also potentially relevant to other developmental processes and to cancer, both of which involve a phenomenon called cell competition. This occurs when two cell populations vie for domination and the losing cells are extruded from the epithelium. Can cell competition be understood as a mixing event between two different nematic liquid crystals? And could the outcome be predicted purely on the basis of differences in the nematic properties of the two populations?

Finally, Saw and colleagues' discovery might help us to understand the epithelial-to-mesenchymal transition (EMT), an early event in cancer progression that is linked to a reduction in intercellular adhesion and an increase in cell motility[11]. Given that both intercellular adhesion and cell motility probably influence the properties of epithelial-cell nematics, it would be intriguing to know how the molecular steps leading to EMT affect such liquid crystals. ■

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MARINE CONSERVATION

The race to fish slows down

A fishery can allow participants to fish as hard as they can until its quota is reached, or allocate quota shares that can be caught at any time. A comparison of the systems in action reveals that shares slow the race to fish. SEE LETTER P.223

ANDREW A. ROSENBERG

A resource available for unlimited common use inevitably tends to be overused and subject to degradation. This is called 'the tragedy of the commons' in a widely read essay[1] that has been influential in natural-resources management, environmental sciences and economics. In fisheries, the tragedy is manifested by fishermen racing to catch all they can before an annual limit is reached, with a fishery then being closed for the remainder of the year. Intensive fishing until the quota is fulfilled can result in a tendency to push fishing operations to the limit, marginalizing other concerns such as habitat protection or safety, and can result, for example, in fishermen being more likely to fish in bad weather (Fig. 1), rather than lose out on their limited chance to fish.