angular momentum of the droplet's horizontal motion: down for clockwise motion and up for anticlockwise motion.

The authors found that when these circular wells are arranged on a one- or two-dimensional lattice with a small (millimetre-scale) lattice spacing, the droplets can be affected by the surface waves emitted by neighbouring droplets (Fig. 1b). Depending on the lattice shape and dimensions, and the experimental conditions, the pattern of droplet spins can resemble the arrangement of magnetic spins in ferromagnetism or antiferromagnetism, meaning that symmetry is broken spontaneously. This ordering of droplet spins emphasizes the complex wave-interaction mechanism that is mediated across the lattice. In spectacular experiments, Sáenz *et al.* discovered that a global angular momentum can be imposed on the system, similar to the way in which an external magnetic field aligns spins and thereby magnetizes materials.

Sáenz and colleagues' work demonstrates that arrays of these droplets can synchronize their bouncing vertical motion just as fireflies synchronize their light flashes. Moreover, it shows that the droplet spins can exhibit pattern formation and symmetry breaking, similar to those seen in magnetic-spin lattices, through subtle hydrodynamic interactions. The system therefore seems to combine the two archetypal models mentioned previously.

Although the hydrodynamic spin lattices presented share many features with magnetic-spin systems, the former are out of equilibrium whereas the latter are in equilibrium, suggesting that the observed synchronized behaviour might be universal. Sáenz and colleagues' experiments used a limited number of bouncing droplets (fewer than 50), but the authors model larger systems that could be explored in future numerical studies. There is little doubt that these hydrodynamic spin lattices will inspire research at the intersection of statistical physics, nonlinear physics and fluid mechanics.

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The author declares no competing interests.

Structural biology

Two giants of cell division in an oppressive embrace

Silke Hauf

The enzymes separase and cyclin-dependent kinase are key orchestrators of cell division. Structural data reveal the surprisingly intricate mechanism that renders them both inactive when bound to each other. **See p.138**

In every dividing cell, a time comes when the two copies of the genome need to be separated. The aptly named enzyme separase springs into action and gets the job done. Unleashing separase at any other time in the life of a cell would be dangerous, so the enzyme is kept well guarded. Human separase is held in check by not one but three mutually exclusive inhibitors. On page 138, Yu *et al.*[1] report structures of human separase in complex with two of these inhibitors. The structures show commonalities but also striking differences. One of the inhibitors snakes along separase to embed itself in the enzyme's active site. The other forces separase to inhibit itself; at the same time, this inhibitor is itself inhibited by separase in an entangled embrace.

Cell division is studied both for its beauty and for the danger that it represents. When all goes well, new healthy cells are born. But when things go awry, newborn cells inherit faulty copies of the genome and might die or become the seed for cancerous growth. Movies of cell division showing this dramatic process never fail to intrigue, and such films have provided an inspiration that has launched renowned scientific careers (see, for example, ref. 2). In the key scene of cell-division movies, chromosomes split abruptly along their length, separating the two copies of

From the archive

An account of the unveiling of the theory of natural selection, and a reported sighting of an unusual type of lightning.

50 years ago

It is a truth of history and an aspect of human behaviour that momentous occasions recalled in later life ... often gain in grandeur and importance with the passing of time. A study of contemporary documents by J. W. T. Moody (*J. Soc. Bibliog. Nat Hist.*, **5**, 474; 1971) shows that the presentation of the Darwin–Wallace papers on natural selection to the scientific world on July 1, 1858, was no exception ... [T]he occasion has been said to represent the beginning of a new era in scientific thinking ... but at the time of its presentation it was something of a non-event. [T]he meeting at the Linnean Society ... had been specially called by the president for the election of a new council member ... [T]he secretary read the text of the Darwin and Wallace papers ... Darwin for domestic reasons did not attend the meeting ...[A]t that date agenda were not sent to members, so the fewer than thirty members who attended ... can hardly have expected a momentous meeting ... Moody ... suggests that the audience were not so much stunned by new ideas as they were overwhelmed by the sheer volume of information loaded upon them. No formal discussion took place at the meeting, the audience was expected to switch its attention instantly from the Darwin–Wallace papers to "Notes on the organization of *Phoronis hippocrepis*".

From *Nature* 6 August 1971

100 years ago

A description of ball lightning seen in the sky at St. John's Wood during a thunderstorm in the early morning of June 26 has recently been received at the Meteorological Office. The phenomenon, a large incandescent mass floating in the air below the clouds and apparently stationary for some minutes, is of great rarity, and the Director of the Meteorological Office, London, S.W.7, would be greatly obliged if persons who observed it on this occasion would communicate with him.

From *Nature* 4 August 1921

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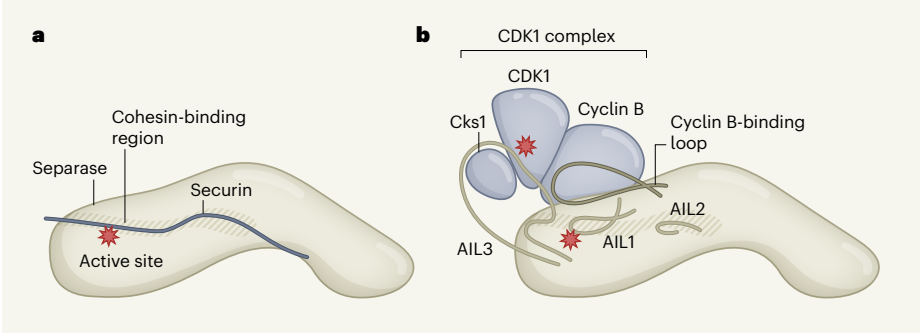

Figure 1 | Structural insights into inhibition of the separase enzyme. When separase cleaves its target substrate, a protein complex called cohesin, this enables chromosome separation to occur. **a**, The protein securin inhibits separase by binding to a region of the enzyme (shaded area) that normally binds to components of cohesin[14]. Securin binding blocks substrate access to the enzyme's active site[7,8]. Consistent with this earlier work in other species, Yu *et al.*[1] present structural data, obtained using cryogenic electron microscopy, indicating that securin inhibits human separase through this same mechanism. **b**, The authors also obtained structural data revealing how the CDK1 complex (which contains the proteins Cks1, CDK1 and cyclin B) inhibits separase. This occurs through a different mechanism, which relies on separase inhibiting itself. Binding of the CDK1 complex triggers three autoinhibitory loops (AIL1, AIL2 and AIL3) in separase to block parts of the substrate-binding site. In addition, CDK1 is inhibited by AIL3, in agreement with previous biochemical analysis[9], and cyclin B is inhibited by a fourth separase loop.

the genome destined for the daughter cells. The major force behind the split is separase, which at this crucial moment cleaves a protein complex called cohesin that serves as 'glue' between the genome copies[3].

Until this pivotal moment, separase activity is blocked by inhibitors. The best-characterized inhibitor is the protein securin, which begins to bind to separase while that enzyme is still being made[4]; it even supports separase synthesis[5]. Genetic and biochemical experiments were the first to hint at the possibility that securin mimics the cohesin substrate and binds to the active site of separase[6]. Structures of budding yeast and nematode separase in complex with securin confirmed this[7,8]. One of the structures solved by Yu *et al.* using cryogenic electron microscopy now shows that the same is true for human separase (Fig. 1).

The big surprise comes with the second structure that Yu *et al.* solved. This shows separase bound to another of its inhibitors, the cyclin-dependent kinase 1 (CDK1) complex, which consists of the proteins Cks1, CDK1 and cyclin B. This complex is itself a major player in cell division, and it functions by phosphorylating (adding phosphate groups to) hundreds, if not thousands, of different proteins to bring about the cellular changes required for division. To solve this structure, the authors used a neat trick[5]: they fused separase to a short piece of securin that was long enough to promote separase synthesis but not so long that it impaired binding of the CDK1 complex.

Despite much previous biochemical insight into the interaction between separase and the CDK1 complex[9], anyone would have been hard-pressed to imagine the structure that Yu *et al.* have solved. The same sites in separase that are used to bind securin are occupied, but now by separase itself, which has become autoinhibitory (Fig. 1). However, unlike securin (and probably cohesin), which binds to separase in a linear fashion (as a continuous stretch of protein), the autoinhibitory elements of separase found in this key binding region are non-contiguous and come from three loops, which the authors call autoinhibitory loops (AIL1, AIL2 and AIL3). AIL3 not only autoinhibits separase; it also inhibits CDK1 by binding to its active site. This loop probably binds to every protein in the complex.

"Anyone would have been hard-pressed to imagine the structure that the authors have solved."

A fourth separase loop wraps around cyclin B and contributes to inhibition of the CDK1 complex. At the centre of this separase loop is a well-characterized phosphorylation site that is required for the formation of this complex[9]. Visualization of this phosphorylation site in the structure revealed a previously unrecognized phosphate-binding pocket in cyclin B. Seeing the strikingly different types of inhibition achieved by securin and the CDK1 complex makes one wonder what sort of inhibition mechanism the third and most recently discovered[10] separase inhibitor, SGO2/MAD2, might have up its sleeve.

Separase inhibition by securin is probably universal across eukaryotes (organisms with a nucleus), but inhibition by the CDK1 complex seems to be vertebrate specific. Why different inhibition modes evolved, and how labour is distributed between these inhibition options, remain mysterious. Some mammalian cell types crucially rely on separase inhibition by the CDK1 complex[11], highlighting the importance of the new structural data that Yu and colleagues report. All three types of separase complex coexist in human cell lines[10]. What determines which inhibitor binds to a given separase molecule, and whether separase molecules bound to the various inhibitors execute different functions in the cell once released from inhibition, is unclear. Separase has other roles in cell division beyond that of cohesin cleavage, and perhaps different inhibitors enable spatial or temporal control of separase activity.

Interestingly, although separase needs to be released from its inhibitors to trigger chromosome separation, the CDK1 complex also binds to separase late during cell division, at a time after separase has become active and cohesin has been cleaved. Inhibition of CDK1 in this complex supports the movement of chromosomes into the daughter cells[12].

The formation of this late complex requires the enzyme PIN1 (ref. 13), which acts on a site in the separase loop that binds to cyclin B. Curiously, assembly of the CDK1 complex bound to separase in the structure that Yu *et al.* solved did not require PIN1. Human separase not only cleaves cohesin, but also cleaves itself when it becomes active. To solve the structure, the authors made separase catalytically inactive to prevent its auto-cleavage. Did this modification alleviate the requirement for PIN1? And is the reported structure of the CDK1 complex bound to separase representative of a complex found early during cell division, but possibly different from that assembled later on?

Clearly, more remains to be uncovered about the regulation of separase. Further behind-the-scenes footage will be needed before we can not only admire, but also fully understand, cell-division movies.

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The author declares no competing interests.
This article was published online on 21 July 2021.

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