alongside other genes involved in evasion of bacterial defences, argues that the nucleases have a key role in preventing bacteria from launching an abortive-infection defence. Hobbs *et al.* confirmed this by demonstrating that Acb1 and Apyc1 interfere with CBASS- and Pycsar-mediated immunity, and they present evidence that phage mutants lacking these nucleases have a greatly reduced ability to evade microbial defences mediated by cyclic nucleotides.

The authors observed that, although Acb1 is relatively nonspecific in terms of its nucleotide targeting, to be effectively cleaved, the target molecule must contain at least one nucleotide that contains the base adenine. It is unknown whether this is due to mechanistic constraints, is the result of phage nucleases having evolved to avoid being quenched by cyclic nucleotides they do not need to target, or is to circumvent an unfavourable physiological response by bacteria during infection. For instance, many bacteria use c-di-GMP to control and coordinate various aspects of cell growth and behaviour[18], and enzymes interfering with this complex regulatory network might therefore perturb optimal phage propagation. Consistent with this, c-di-GMP seems to be used as a defence signal only by specific groups of bacteria that do not exploit this molecule for their own cellular regulation[16]. Nevertheless, the interplay between host- and phage-mediated control of nucleotide messengers remains poorly understood. Hobbs *et al.* observed that structurally related versions of Apyc1 are encoded in bacterial genomes. This raises the possibility that these function to actively regulate Pycsar defences, or that other regulatory networks harnessing nucleotide second messengers await discovery.

Hobbs and colleagues' findings add to a growing list of viral components that interfere with cyclic nucleotide defence signals in the various kingdoms of life. This list includes poxins[19] — nucleases from mammalian viruses called poxviruses that obstruct the cGAS–STING pathway by degrading 2′,3′-cGAMP — as well as viral nucleases that degrade molecules called cyclic oligoadenylates, to interfere with defences (mediated by a mechanism known as CRISPR) in microorganisms called archaea[20].

One could speculate that the remarkable diversification of nucleotide second messengers in bacteria is crucial for maintaining antiphage defences in the face of constant evolutionary pressure by their phage predators. Indeed, no single type of phage investigated by Hobbs *et al.* could degrade all known cyclic nucleotides involved in bacterial defence, despite the broad substrate specificities of the phage nucleases. Given the growing list of bacterial defence mechanisms being discovered, and the possibility that these represent a limiting factor in the development of therapies that harness phages to combat bacterial infections, then engineering phages to have broader nuclease activities might be a suitable way to equip these viruses with maximal and far-reaching antimicrobial capacity.

Urs Jenal is at the Biozentrum, University of Basel, CH-4056 Basel, Switzerland.
e-mail: urs.jenal@unibas.ch

1. Hobbs, S. J. *et al. Nature* **605**, 522–526 (2022).
2. Sutherland, E. W. & Robison, G. A. *Pharmacol. Rev.* **18**, 145–161 (1966).
3. Ross, P. *et al. Nature* **325**, 279–281 (1987).
4. Witte, G., Hartung, S., Büttner, K. & Hopfner, K.-P. *Mol. Cell* **30**, 167–178 (2008).
5. Davies, B. W., Bogard, R. W., Young, T. S. & Mekalanos, J. J. *Cell* **149**, 358–370 (2012).
6. Cohen, D. *et al. Nature* **574**, 691–695 (2019).
7. Sun, L., Wu, J., Du, F., Chen, X. & Chen, Z. J. *Science* **339**, 786–791 (2013).
8. Ablasser, A. *et al. Nature* **498**, 380–384 (2013).
9. Wu, J. *et al. Science* **339**, 826–830 (2013).
10. Burdette, D. L. *et al. Nature* **478**, 515–518 (2011).
11. Hopfner, K.-P. & Hornung, V. *Nature Rev. Mol. Cell Biol.* **21**, 501–521 (2020).
12. Wein, T. & Sorek, R. *Nature Rev. Immunol.* https://doi.org/10.1038/s41577-022-00705-4 (2022).
13. Whiteley, A. T. *et al. Nature* **567**, 194–199 (2019).
14. Ye, Q. *et al. Mol. Cell* **77**, 709–722 (2020).
15. Govande, A. A., Duncan-Lowey, B., Eaglesham, J. B., Whiteley, A. T. & Kranzusch, P. J. *Cell Rep.* **35**, 109206 (2021).
16. Morehouse, B. R. *et al. Nature* **586**, 429–433 (2020).
17. Tal, N. *et al. Cell* **184**, 5728–5739 (2021).
18. Jenal, U., Reinders, A. & Lori, C. *Nature Rev. Microbiol.* **15**, 271–284 (2017).
19. Eaglesham, J. B., Pan, Y., Kupper, T. S. & Kranzusch, P. J. *Nature* **566**, 259–263 (2019).
20. Athukoralage, J. S. *et al. Nature* **577**, 572–575 (2020).

The author declares no competing interests.
This article was published online on 29 April 2022.

Developmental biology

Tension around the clock

Miki Ebisuya & Xavier Trepat

The formation of body segments in vertebrate embryos has long been attributed to the spatio-temporal patterning of molecular signals. But segment length in zebrafish is now found to be adjusted by tissue mechanics. **See p.516**

Not all clocks are precise. The segmentation clock is a molecular oscillator that regulates the timing of the formation of somites — multicellular blocks that give rise to bilateral structures such as ribs and skeletal muscle. During vertebrate development, somites periodically bud off on both sides of an embryonic structure called the neural tube[1], with one pair of somites being formed during each cycle of the segmentation clock. The somites' initial volume is determined by both the frequency of the clock's oscillation and the speed of cell movement[2]. But Naganathan and colleagues[3] reveal on page 516 that the initial length of somites is surprisingly imprecise. The authors uncover a mechanism by which length is adjusted during somite formation in zebrafish. Rather than being based on the segmentation clock, this mechanism hinges on a single mechanical property of the somite — its surface tension.

"These findings imply a contribution of tissue mechanics to the symmetrical appearance of somites."

Using sophisticated 3D imaging of zebrafish embryos, Naganathan *et al.* first observed that the head-to-tail (antero-posterior) length of newly formed somites was highly variable. However, over the course of two hours, the somites adjusted to a target length of 51 micrometres.

The authors considered several potential mechanisms to explain this length adjustment. First, they tested whether it could be understood through the effects of the segmentation clock. They ruled out this possibility by showing that perturbing the clock did not change the dynamics of length adjustment. Second, they considered mechanisms based on crosstalk between left and right somites. Again, they ruled this out, showing that disrupting somite formation on just one side of the embryo did not affect length adjustment on the other side. A third possibility was that the length adjustment could be explained by differential overall growth rates in somites. But this possibility, too, was rejected when the authors showed that somite volume remained constant during length adjustment. Instead, they found that changes in the antero-posterior length of the somites were balanced by changes in the centre-to-side (mediolateral) length.

Naganathan and co-workers then proposed that the adjustment of somite length is driven by a mechanical property of the somite, namely,

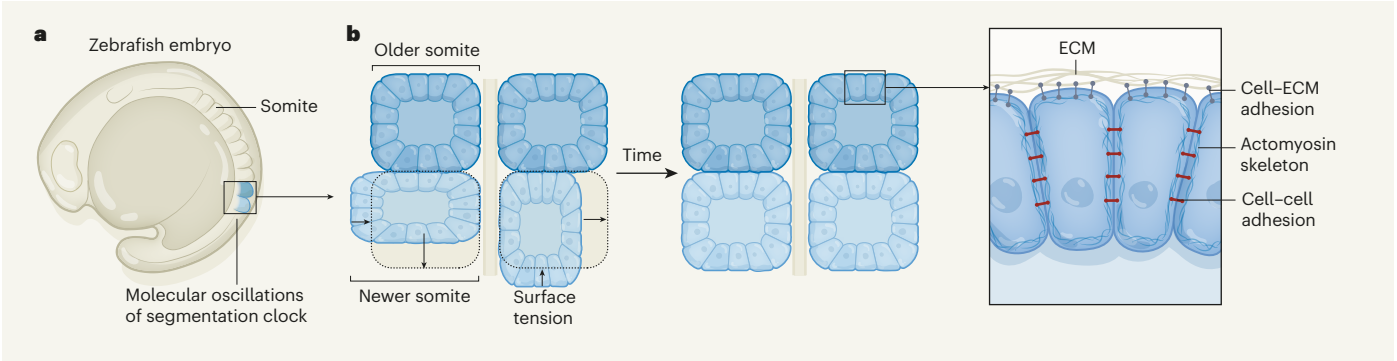

Figure 1 | Adjustment of somite length by surface tension. a, During a period of zebrafish development called segmentation, structures called somites are formed periodically, from head to tail, driven by a molecular oscillator called the segmentation clock. **b**, Naganathan *et al.*[3] show that newly formed somites are highly variable in length (but have the same volume, determined by the segmentation clock). This length is adjusted by means of somite surface tension, ensuring left–right symmetry. Somite surface tension arises from a network of structural actomyosin proteins in the internal 'skeleton' of the somite cells, from cell–cell adhesion and from cell–extracellular matrix (ECM) adhesion in the somites. (Only the outermost cell layer of somites is depicted, for simplicity.)

its surface tension. The role of surface tension in somites can be understood by analogy with the intuitive mechanics of a fluid droplet. When the droplet is squeezed between two parallel, non-sticky surfaces, it will deform to a length imposed by the separation between the surfaces. But, after sudden removal of the squeeze, it will adopt its original, spherical shape. The rate at which the droplet regains its spherical form will depend mainly on its surface tension (which tends to speed the process up) and its viscosity (which tends to slow it down).

Much like a fluid droplet, somites also display a tension at their surface and a viscosity in their bulk. But the origin of these physical properties is more complex than in the simple fluid droplet. Tension at the surface of somites arises from a variety of processes, including the contractility of their cells' internal 'skeleton' (which consists of actomyosin protein filaments) and the adhesion between individual cells, and between cells and the extracellular matrix (ECM)[4]. By contrast, viscosity arises mainly from the sliding, turnover and attachment kinetics of cell–cell and cell–ECM adhesions in the somite bulk.

Naganathan *et al.* established that somites indeed behave like a fluid with a surface tension, showing that they rounded up when isolated from an embryo as an explant, and that the cells in the somite bulk displayed diffusive dynamics. The timescale of rounding had the same order of magnitude as the process of length adjustment. Moreover, perturbing the actomyosin cytoskeleton, cell–cell adhesion and cell–ECM adhesion slowed down the rounding of somite explants, and impaired the antero-posterior length adjustment in embryos. This evidence — together with a mechanical model that incorporates stresses applied to somite boundaries — indicates that surface tension adjusts antero-posterior length in newly formed somites (Fig. 1).

These findings imply a contribution of tissue mechanics to the symmetrical appearance of somites on the left and right sides of the neural tube. Because somites become bilateral structures, their left–right symmetry is crucial. This symmetry has been attributed historically either to the symmetrical formation of somites (ensured by the precision of the segmentation clock) or to left–right crosstalk[5]. But both mechanisms are inconsistent with the new findings, which suggest that symmetry arises unilaterally: the robustness of somite surface tension, combined with boundary stresses in the system, ensures that somites from both sides adjust to the same target length and so produce left–right symmetry.

Naganathan and colleagues' proposed mechanism raises several questions and expectations. For instance, even after surface tension reduces the initial heterogeneity in somite length, this variability will eventually increase again as somites develop into bilateral skeletons and muscles. Is there an extra mechanism — mechanical or non-mechanical — that puts limits on the increasing variability in later stages, or a crosstalk mechanism between the left and right somite derivatives?

The paper also raises intriguing questions about the material properties of the presomitic mesoderm tissue from which somites arise, and its role in somite formation. Previous work[6] established that the mesoderm is in a solid-like state during somite formation, which would seem inconsistent with the fluid behaviour reported by Naganathan and co-workers. These observations might be reconciled if mechanical stress is generated that transiently fluidizes the tissue during somite formation. Potential sources of such stress are the contractile ring that separates adjacent somites, and the active fluctuations in tension at cell–cell contacts[7].

Finally, Naganathan and colleagues have focused on zebrafish, but studying somite surface tension and left–right symmetry in other species will be of interest, especially given that the zebrafish segmentation clock is much faster than those of its mammalian counterparts[1], and that fish somites adopt a specific V shape at later stages[8]. Live imaging and mechanical manipulation of mammalian somite formation is challenging. But recent advances in *in vitro* models using stem cells could open a way to compare somite mechanics across species[9,10].

Miki Ebisuya is at the European Molecular Biology Laboratory (EMBL) Barcelona, 08003 Barcelona, Spain. **Xavier Trepat** is at the Catalan Institution for Research and Advanced Studies, Institute for Bioengineering of Catalonia, Barcelona Institute for Science and Technology and the Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine, 08028 Barcelona, Spain.
e-mails: miki.ebisuya@embl.es; xtrepat@ibecbarcelona.eu

1. Hubaud, A. & Pourquié, O. *Nature Rev. Mol. Cell Biol.* **15**, 709–721 (2014).
2. Oates, A. C., Morelli, L. G. & Ares, S. *Development* **139**, 625–639 (2012).
3. Naganathan, S. R., Popović, M. & Oates, A. C. *Nature* **605**, 516–521 (2022).
4. Amack, J. D. & Manning, M. L. *Science* **338**, 212–215 (2012).
5. Guillon, E. *et al. eLife* **9**, e48964 (2020).
6. Mongera, A. *et al. Nature* **561**, 401–405 (2018).
7. Shelton, E. R. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.03.27.437325 (2021).
8. Tlili, S. *et al. Proc. Natl Acad. Sci. USA* **116**, 25430–25439 (2019).
9. van den Brink, S. C. *et al. Nature* **582**, 405–409 (2020).
10. Veenvliet, J. V. *et al. Science* **370**, eaba4937 (2020).

The authors declare no competing interests.
This article was published online on 27 April 2022.