

Embryo geometry sets the tempo

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The geometry of the zebrafish egg is shown to generate a gradient in cell size upon successive cell divisions. This gradient specifies stereotyped patterns of cell-cycle progression, zygotic genome activation and cell-fate specification.

Eggs come in a variety of shapes and internal organization. Human oocytes are round, insect eggs tend to be more elongated, and those of fishes and birds consist of a flat single cell – the blastodisc – perched atop a vast yolk sac. Whether such geometrical variations help in guiding embryonic development has remained unclear. Now, writing in *Nature Physics*, Nikhil Mishra and colleagues¹ have revealed that in the zebrafish embryo, the curvature of the yolk–blastodisc interface shapes the geometry of individual cells, leading them to divide asymmetrically, with important consequences for subsequent embryo development.

The early development of most animal species is characterized by exceptionally rapid cell divisions that transform the one-cell egg into a multicellular entity. The pace of these divisions is governed by the cell cycle, an internal biochemical clock driven by oscillations in the levels of specific proteins that control cell-cycle progression. In most embryos, cell cycles are initially synchronized across all cells, but gradually slow down and desynchronize in later stages. During the transition phase from synchrony to asynchrony, cells often accumulate

small but regular phase delays with respect to their neighbours, leading to the emergence of meta-synchronous cell-cycle oscillations and the propagation of mitotic waves that travel across embryos.

Remarkable examples of these waves have been described in *Drosophila* embryos and *Xenopus* cytoplasm extracts^{2,3}, which are both syncytial systems, so that all nuclei are bathed in one common cytoplasm. Mitotic waves emerge as a result of reaction diffusion and positive feedback in the cell-cycle regulation complex, rapidly amplifying the diffusible mitotic signals travelling from one dividing nucleus to the next one. This creates a wave front that propagates much faster than diffusion, keeping cell cycles in near synchrony across distances of several hundreds of micrometres, the size scale typical of early embryos. Key to the formation of these waves is that cell-cycle-regulating molecules can diffuse from one nucleus to the next, because of the lack of physical boundaries separating nuclei in these syncytia.

Mishra and colleagues monitored cell-cycle progression with microscopy in the zebrafish embryo. They reported a metasynchronous phase, from the second division cycle to the ninth, preceding complete asynchrony¹. Strikingly, this phase was marked by the propagation of eight consecutive mitotic waves travelling from the animal pole to the yolk margin. However, and in contrast to the syncytial systems described above, these waves form despite membrane boundaries separating the cycling nuclei. The team investigated the mechanism behind mitotic wave formation. Using a combination of experimental assays, they showed that there was no coupling between cells. They also implemented a Kuramoto model of phase-coupled oscillators, to

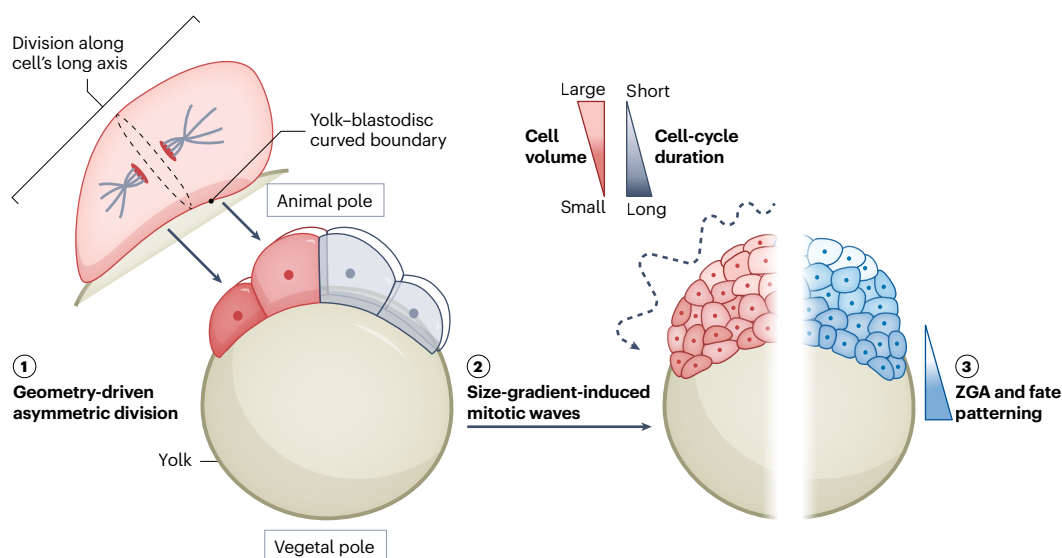


Fig. 1 | From cell division geometry to cell-cycle dynamics and fate patterning in the early zebrafish embryo. On the left, a schematic of an 8-cell-stage zebrafish embryo illustrates how asymmetric cell divisions generate smaller cells at the periphery of the blastodisc (shown in darker red). This asymmetry arises from mother cells bisecting their long axis during division while conforming

to the curved surface of the yolk. On the right, a schematic of a 128-cell-stage zebrafish embryo shows how the propagated cell volume gradient (red gradient) drives the emergence of mitotic waves (blue gradient), and how this contributes to the spatial patterning of zygotic genome activation (ZGA) and the acquisition of early cell fates (cyan gradient).

demonstrate that mitotic waves could only be predicted by weak and decaying cell–cell coupling strength. If cells are uncoupled, preventing the diffusion of mitotic signals across neighbours, it is unclear how they can accumulate regular phase delays to trigger mitotic waves.

Mishra and colleagues proposed that this cell-autonomous regulation of cell-cycle duration was driven by a gradient in the nuclear-to-cytoplasm volume ratio. The gradient was set by variations in cell volumes, with larger cells that cycle faster located near the animal pole and smaller cells that cycle more slowly located near the yolk margin. This hypothesis was supported by experimental manipulations of the nuclear-to-cytoplasm ratios that directly modulate cell-cycle duration. Moreover, the team provided evidence that this volume gradient originated from early asymmetric divisions at the 4-cell and 8-cell stages. In addition to its impact on cell-cycle timing, this gradient also patterned fundamental aspects of early development, including zygotic genome activation (re-expression of the newly assembled genome), and cell-fate specification (Fig. 1).

The study by Mishra and colleagues raises fundamental questions for cell and developmental biology. First, their proposition that cells divide asymmetrically by bisecting the longest cell axis, while adopting an anisotropic shape, suggests a new mechanism for division plane positioning based on cellular length sensing (rather than volume sensing, as was previously proposed)^{4,5}. Therefore, an interesting question is whether, in these early zebrafish cells, the contractile ring that cleaves the cell may readjust its position to the middle of the cell length, by sliding towards the thinner part of the cell as it contracts, for example⁶.

Second, the notion that cell size, and therefore the nucleus-to-cytoplasm ratio, directly alters cell-cycle duration is supported by an increasing amount of evidence across systems⁷. However, a puzzling observation is that in the zebrafish embryo, cell-cycle durations are nearly constant until the eighth round of division, in spite of drastic changes in cell volumes⁸. This raises the question of whether cell-size effects on the cell cycle may only operate above a certain threshold in size or nuclear-to-cytoplasm ratio, or whether they are mostly associated with asymmetries in this ratio among neighbours. It is also important to note that additional mechanisms

that cannot scale with cell size – such as the partitioning of specific endomembranes or the transcription of a subset of zygotic genes – may interfere with a direct regulation of cell-cycle duration based on nuclear-to-cytoplasm ratio^{9,10}.

Finally, a major result of this study is to show that cell size and nuclear-to-cytoplasm ratio also instruct zygotic genome activation and fate specification. Whether size directly affects these processes or whether they are an indirect consequence of cell-cycle modulations by cell size remain fundamental, open questions. In that context, it is remarkable that the relatively noisy pattern of cell sizes reported by Mishra and colleagues can converge onto sharp gradients in zygotic genome activation and fate specification.

Overall, Mishra and colleagues provide a striking example of how geometrical constraints during early embryonic divisions can be transduced into fate patterning. Given the large diversity in egg geometries and sizes found among animal species, the study may help to uncover fundamental connections between embryo architecture, cell division and developmental regulation.

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References

1. Mishra, N., Li, Y. I., Hannezo, E. & Heisenberg, C.-P. *Nat. Phys.* <https://doi.org/10.1038/s41567-025-03122-1> (2026).
2. Deneke, V. E. et al. *Dev. Cell* **38**, 399–412 (2016).
3. Chang, J. B. & Ferrell, J. E. Jr *Nature* **500**, 603–607 (2013).
4. Minc, N. et al. *Cell* **144**, 414–426 (2011).
5. Jimenez, A. J. et al. *Curr. Biol.* **31**, 1206–1220 (2021).
6. Cabernard, C. et al. *Nature* **467**, 91–94 (2010).
7. Balachandra, S. et al. *Ann. Rev. Genet.* **56**, 165–185 (2022).
8. Olivier, N. et al. *Science* **329**, 967–71 (2010).
9. Mukherjee, R. N. et al. *Dev. Cell* **54**, 395–409 (2020).
10. Gentsch, G. E. et al. *iScience* **16**, 485–498 (2019).

Competing interests

The authors declare no competing interests.