CellPress

Current Biology

Dispatches

Cell cycle: Making waves to coordinate the entry into mitosis

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https://doi.org/10.1016/j.cub.2022.10.030

How do very large cells coordinate their entry into mitosis? A new study shows that the bistability of the Cdk/Cyclin system allows cells to generate either 'trigger waves' or 'sweep waves' that drive cells into mitosis in different ways with distinct consequences.

The early embryos of many metazoans, including fish, frogs and flies, are very large (~0.5–1.2mm), and they begin life by proceeding through a rapid series of near-synchronous divisions[1]. Anyone who has seen time-lapse movies of these embryos can't help but marvel at their speed and coordination — how do they divide so quickly, and how are their divisions so tightly synchronised across such large distances? This coordination is particularly striking in the early embryo of the fruit fly *Drosophila melanogaster*. Unlike frog and fish embryos, which comprise separate dividing cells, the nuclei in fly embryos undergo 13 rounds of near-synchronous division within a giant single cell (a syncytium)[2]. In these embryos, the nuclei usually enter mitosis in 'waves' that start at both poles and rapidly spread towards the middle (Figure 1A).

Previous experiments and modelling have indicated that a wave-like spreading mechanism can explain the coordinated entry into mitosis in the large single cell of the newly fertilised *Xenopus laevis* embryo[3]. Mathematical modelling revealed that the combination of positive and negative feedback loops that regulate Cdk/Cyclin activity constitute a bistable system[4,5]. Prior to cell division, Cdk/Cyclin generally occupies the relatively low-activity state, but, as Cdk/Cyclin activity starts to rise globally in preparation for mitosis, the Cdk/Cyclin activity in a small local region of the cell will cross a threshold and enter the high-activity state. This may be due to stochastic noise in the system, or the presence of an organelle such as the nucleus, where Cdk/Cyclin activity may be inherently slightly higher[6]. The high-activity Cdk/Cyclin molecules in these regions can then diffuse and convert nearby Cdk/Cyclin molecules to the high-activity state. This creates a wave of activation that propagates across the cell at speeds of ~60 μm/min, ensuring that the whole cell is converted to the stable high-activity mitotic state in a coordinated manner. This diffusion-driven activation of Cdk1 is known as a 'trigger wave'[3].

Looking at the waves of mitosis that spread across the early *Drosophila* embryo, it seems intuitively obvious that they must by generated by a similar trigger-wave mechanism. Surprisingly, however, in a series of papers in which the authors have tracked, perturbed and modelled the mitotic waves in *Drosophila* embryos[7–9] (including a new report by Hayden *et al.*[10], in this issue of *Current Biology*), Di Talia and colleagues conclude that this is not the case. Although a similar bistable Cdk/Cyclin circuitry exists in *Drosophila* embryos, trigger waves cannot explain the dynamics of mitotic entry. Not only are trigger waves too slow to account for these rapid dynamics, but careful analysis with a FRET-reporter of Cdk/Cyclin activity revealed that the wave of mitosis-inducing activity that one assumes must be spreading through the embryo is only an illusion — Cdk/Cyclin activity actually rises at a uniform rate across the entire embryo simultaneously. The illusion is created by inhomogeneities in Cdk/Cyclin activity that exist prior to the entry into mitosis. That is, some areas of the embryo (presumably normally located close to the poles) have intrinsically higher levels of Cdk/Cyclin activity from the very beginning of each nuclear cycle. These differences are then simply maintained as the whole embryo is swept into mitosis by a rapid global rise in Cdk/Cyclin activity, which the authors term a 'sweep wave'[9].

Crucially, in the theoretical/mathematical framework used by Di Talia and colleagues, trigger waves and sweep waves are two manifestations of the same underlying Cdk/Cyclin bistability system[9]. If the entry into mitosis is driven relatively slowly, then diffusion dominates the activation of the system because any locally activated Cdk/Cyclin molecules will have time to diffuse and activate nearby molecules. This forms a trigger wave that can propagate and induce mitotic entry through the entire embryo. If, however, the entry into mitosis is driven quickly, then the rapid activation dominates the system, as any Cdk/Cyclin molecules activated above the bistability threshold will not have time to diffuse and activate molecules throughout the rest of the embryo. In this latter scenario, any gradient in Cdk/Cyclin activity that existed prior to mitosis will tend to be maintained as Cdk/Cyclin activity rises rapidly and uniformly throughout the embryo in a sweep wave.

A key prediction of this model is that the *Drosophila* embryo sweep-wave regime can be converted to a trigger-wave regime if the drive into mitosis is sufficiently slowed. In the new paper, Hayden *et al.*[10] show that this is indeed the case. In embryos in which the dosage of the key Cdk/Cyclin activator Polo/PLK1 has been reduced, the entry into mitosis is dramatically slowed, and in some of these embryos Cdk/Cyclin activation is now propagated as a classical trigger wave. This, and several other experiments,

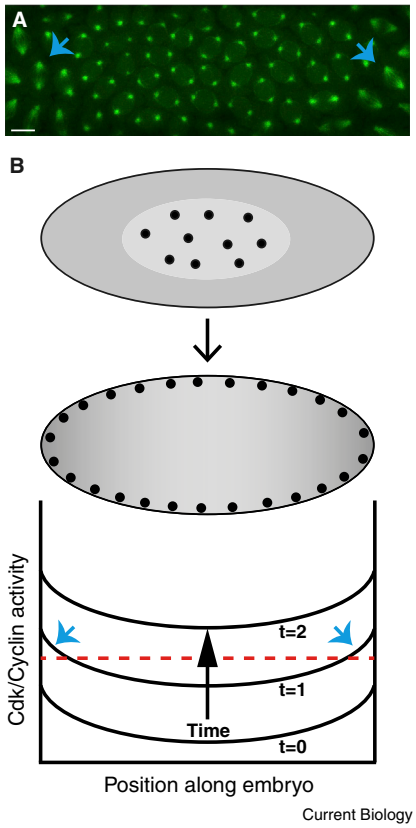

Figure 1. Mitotic waves in the early *Drosophila* embryo.
(A) Image shows the microtubules (*green*) surrounding the nuclei at the cortex of a *Drosophila* embryo. Anterior pole is to the left and posterior to the right. The nuclei enter mitosis (judged by mitotic spindle formation, *blue arrows*) in a wave that starts at the poles and spreads to the middle. Scale bar = 10 μm. (B) Top schematic illustrates an early syncytial embryo (oval) with its nuclei (black dots) clustered in the middle. Cyclin B (grey) is degraded locally around the nuclei at the end of mitosis, potentially creating a central region of relatively low Cyclin B concentration (lighter grey shading). Diffusion can equalise the Cyclin B gradient at the local scale, but not across the whole embryo, which is too large. Thus, when the nuclei reach the embryo cortex (bottom schematic), the Cyclin B concentration is slightly higher at the poles. The bottom graph illustrates how the activity of Cdk/Cyclin B might vary across the length of the embryo at three different time points as a sweep wave causes Cdk/Cyclin activity to uniformly rise across the embryo. At t = *0*, Cdk/Cyclin activity is highest at the poles, but is still below the threshold required to trigger the entry into mitosis (indicated by *red-dashed line*). At t = *1*, Cdk/Cyclin activity has been uniformly swept upwards throughout the embryo. The nuclei at the poles cross the Cdk/Cyclin activity threshold (*blue arrows*) and enter mitosis; the nuclei in the middle remain in interphase. At t = *2* Cdk/Cyclin activity has continued to sweep upwards. The activated Cdk/Cyclin molecules at the poles have not had time to diffuse to activate nearby Cdk/Cyclin molecules, which are instead driven above the activity threshold by the global upward sweep in Cdk/Cyclin activity; all the nuclei are now in mitosis. In this way a 'wave' of mitosis appears to spread from the poles, even though no information has physically spread from one region to the other. Image in (A) courtesy of Siu-Shing Wong.

strongly supports the authors' contention that the two wave types can be understood as distinct outcomes of the same theoretical framework in which the differentiating factor is the rate at which the entry into mitosis is driven. A remarkable conclusion from this body of work is that the coordinated waves of mitosis that appear to spread across the early fly embryo are actually not synchronised by any mechanism that actively passes information across the embryo.

If this is the case, then why do early fly embryos enter mitosis in such a reproducible and spatially synchronised manner? One possible explanation is that the localised destruction of Cyclin B around the nuclei in these embryos can create relatively reproducible gradients in Cyclin B concentration across the embryo (Figure 1B). In early fly embryos, Cyclin B is not degraded globally at the end of mitosis[11,12], but rather is degraded locally on the mitotic spindles[13,14]. As the nuclei initially cluster in the middle of the embryo, this could create a Cyclin B concentration gradient (Figure 1B, top embryo). This gradient would be smoothed by diffusion at the local scale (ensuring that nearby nuclei experience similar Cyclin B concentrations and so enter mitosis at the same time) but maintained at the embryonic scale (as diffusion is too slow to smooth them over such a large distance). Thus, the nuclei that migrate to the polar regions may enter a region that tends to have slightly higher Cyclin B concentrations, and so tend to enter mitosis slightly before the nuclei in the middle of the embryo (Figure 1B, bottom embryo). Once such a gradient of mitotic entry is established, it could be maintained during subsequent cortical divisions, as the nuclei at the poles will exit mitosis before the nuclei in the middle, and so will locally start to accumulate Cyclin B earlier. Diffusion remains too slow to smooth the resulting Cyclin B gradient over the short cortical division time-scale and the large embryonic distance-scale.

The discovery of sweep waves raises some interesting questions about the coordination of cell division[15]. It reveals that cellular events can appear to be spatially and temporally synchronised without the need for an active mechanism that spreads information across the cell. Instead, the establishment of gradients of Cdk/Cyclin activity may be sufficient to spatially order subsequent mitotic events, provided that cells are driven through mitosis fast enough that diffusion effects become negligible. Although cell cycle timing is relatively slow in somatic cells, the entry into mitosis is usually driven quickly. So, sweep waves could theoretically exist in these cells if mitotic entry is fast enough and Cdk/Cyclin diffusion is slow enough. Interestingly, Cyclin B exhibits a complex dynamic distribution during mitosis, so transient local concentration gradients could be formed[16]. In a sweep-wave regime, these gradients could play a role in determining the relative timing of the local activation and inactivation of Cdk/Cyclin. As in the fly embryo, this could give the illusion that these events are tightly synchronised when no information is actually spreading through the cell.

Finally, it is worth highlighting that neither trigger waves nor sweep waves can readily explain how the multiple cells in early frog or fish embryos coordinate their division. The cells in these embryos are presumably not directly interconnected after they divide, and so have no obvious means of communication to coordinate their entry into mitosis. Some sort of mechanical coupling is an obvious possibility, but the *Drosophila* embryo data reveal an interesting alternative: perhaps these cell divisions only *appear* to be actively synchronised. Cyclin B is the dominant driver of mitotic entry in frog embryos[17,18]. Perhaps the mechanisms that regulate the rate of Cyclin B accumulation and destruction are so robust that the rate of cell division hardly deviates between daughter cells, even though there is no mechanism that actively maintains their synchrony.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. O'Farrell, P.H., Stumpff, J., and Su, T.T. (2004). Embryonic cleavage cycles: How is a mouse like a fly? Curr. Biol. *14*, R35–R45.
2. Foe, V.E., and Alberts, B.M. (1983). Studies of nuclear and cytoplasmic behaviour during the five mitotic cycles that precede gastrulation in Drosophila embryogenesis. J. Cell Sci. *61*, 31–70.
3. Chang, J.B., and Ferrell, J.E. (2013). Mitotic trigger waves and the spatial coordination of the Xenopus cell cycle. Nature *500*, 603–607.
4. Novak, B., and Tyson, J.J. (1993). Numerical analysis of a comprehensive model of M-phase control in Xenopus oocyte extracts and intact embryos. J. Cell Sci. *106*, 1153.
5. Tyson, J.J., and Novak, B. (2015). Bistability, oscillations, and traveling waves in frog egg extracts. Bull. Math. Biol. *77*, 796–816.
6. Afanzar, O., Buss, G.K., Stearns, T., and Ferrell, J.E., Jr. (2020). The nucleus serves as the pacemaker for the cell cycle. eLife *9*, e59989.
7. Deneke, V.E., Melbinger, A., Vergassola, M., and Di Talia, S. (2016). Waves of Cdk1 activity in S phase synchronize the cell cycle in Drosophila embryos. Dev. Cell *38*, 399–412.
8. Deneke, V.E., Puliafito, A., Krueger, D., Narla, A.V., De Simone, A., Primo, L., Vergassola, M., De Renzis, S., and Di Talia, S. (2019). Self-organized nuclear positioning synchronizes the cell cycle in Drosophila embryos. Cell *177*, 925–941.e17.
9. Vergassola, M., Deneke, V.E., and Di Talia, S. (2018). Mitotic waves in the early embryogenesis of Drosophila: Bistability traded for speed. Proc. Natl. Acad. Sci. USA *115*, E2165–E2174.
10. Hayden, L., Hur, W., Vergassola, M., and Di Talia, S. (2022). Manipulating the nature of embryonic mitotic waves. Curr. Biol. *32*, 4989–4996.
11. Edgar, B.A., Sprenger, F., Duronio, R.J., Leopold, P., and O'Farrell, P.H. (1994). Distinct molecular mechanism regulate cell cycle timing at successive stages of Drosophila embryogenesis. Genes Dev. *8*, 440–452.
12. Su, T.T., Sprenger, F., DiGregorio, P.J., Campbell, S.D., and O'Farrell, P.H. (1998). Exit from mitosis in Drosophila syncytial embryos requires proteolysis and cyclin degradation, and is associated with localized dephosphorylation. Genes Dev. *12*, 1495–1503.
13. Huang, J., and Raff, J.W. (1999). The disappearance of cyclin B at the end of mitosis is regulated spatially in Drosophila cells. EMBO J. *18*, 2184–2195.
14. Raff, J.W., Jeffers, K., and Huang, J.-Y. (2002). The roles of Fzy/Cdc20 and Fzr/Cdh1 in regulating the destruction of cyclin B in space and time. J. Cell Biol. *157*, 1139–1149.
15. Pines, J., and Hagan, I. (2011). The Renaissance or the cuckoo clock. Philos. Trans. R. Soc. B Biol. Sci. *366*, 3625–3634.
16. Clute, P., and Pines, J. (1999). Temporal and spatial control of cyclin B1 destruction in metaphase. Nat. Cell Biol. *1*, 82–87.
17. Murray, A.W., and Kirschner, M.W. (1989). Cyclin synthesis drives the early embryonic cell cycle. Nature *339*, 275–280.
18. Murray, A.W., Solomon, M.J., and Kirschner, M.W. (1989). The role of cyclin synthesis and degradation in the control of maturation promoting factor activity. Nature *339*, 280–286.

Ensemble perception: Stacking the hay to find the needle

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https://doi.org/10.1016/j.cub.2022.09.042

The visual clutter we constantly encounter in the world limits object recognition, a phenomenon known as visual crowding. A new study shows that ensemble perception counters this by condensing redundant information into summary statistical representations, which thus releases visual crowding's effect on individual objects.

The visual world is a cluttered place; every visual scene is rife with features and objects of all kinds. The very richness of typical visual scenes is problematic, however, as it is potentially overwhelming for the human visual system. One of the manifestations of the torrent of clutter in the visual field is a perceptual phenomenon known as 'visual crowding'[1–3]. Crowding is a ubiquitous effect in which features and objects appear jumbled together in the presence of nearby features and objects (Figure 1A). Along with the rampant clutter in the visual world — and its associated crowding effects — the usual existence of multiple similar objects and features means there is generally a great deal of redundancy in natural scenes. For example, consider collections of leaves in a tree, groups of faces in an audience, runners in a marathon, and so on. Fortunately, the visual system is able to harness these redundancies by encoding the ensemble or summary statistical information that is present in these scenes[4]. Thus, ensemble perception allows us to perceive average features such as color, motion, shape, and facial expressions of crowds (Figure 1B). Ensemble perception is an efficient heuristic to access group-level information at a quick glance, without the need to scrutinize every individual object. A paper in this issue of *Current Biology* by Tiurina *et al.*[5] demonstrates that these