Developmental biology

Unravelling how plant cells divide and differ

Ikram Blilou

In a multicellular organism, normal growth requires control of cell division to generate cells that are similar to or different from their parents. Analysis of this process in plant roots reveals how this mechanism is regulated. **See p.611**

In a developing tissue, asymmetric (also known as formative) cell division is essential to generate specialized cells with distinct functions — something that is crucial for forming diverse tissues and organs. Symmetric (also called proliferative) cell division, producing identical cell types, is required for cells to proliferate and contribute to growth. On page 611, Winter *et al.*[1] provide insights into how these two types of cell division that drive patterning and growth are coordinated.

The authors studied this process in the roots of the plant *Arabidopsis thaliana*, focusing on two proteins, SHR and SCR, which are core plant-specific developmental regulators. These two transcription factors are key determinants for asymmetric cell division. Stem cells divide and can give rise to different types of cell, and SHR and SCR associate physically to form a protein complex that promotes asymmetric cell division of stem cells by controlling the activity of the cell-cycle regulator protein encoded by the gene *CYCD6* (refs 2–5).

The action of the SHR–SCR complex is regulated by the protein RBR (ref. 3). In differentiated cells, RBR binds to SHR–SCR and disrupts its function[3]. In stem cells, RBR is phosphorylated (has phosphate groups attached to it) by the cell-cycle regulator proteins CYCD6 and CDKB1, which prevents the protein from binding to SHR–SCR. This means that the asymmetric cell division controlled by SHR–SCR occurs only in stem cells[3].

This regulatory network acts as a 'bistable' switch in which distinct states of SHR–SCR activity control whether asymmetric cell division occurs[3]. These states are regulated by the gradients in concentration of the molecule auxin and SHR. There is a 'longitudinal' gradient along the direction of the root established by the distribution of auxin (Fig. 1a)[6]. There is a 'radial' gradient running from the centre of the roots to the outer layers; it is put in place by the movement of SHR from the inner vasculature tissue to the outer layer of the root[5]. The two gradients converge to drive the action of SHR–SCR on CYCD6. SHR–SCR activates CYCD6, and auxin increases its expression in stem cells, which leads to RBR phosphorylation and asymmetric cell division.

Although the convergence of the two gradients in a specific cell triggers cell division, protein degradation immediately after the division turns the switch off (generating a low state of SHR–SCR) to prevent further divisions. The bistable switch explains why asymmetric cell division occurs at a specific time and in a specific place to generate distinct cell types and hence specific tissue lineages, a concept that is well established in studies of animal cells[7].

Winter and colleagues' work provides fresh insights into the importance of SHR–SCR in cell-cycle control and highlights its contribution to determining how cells orient the way in which they divide (the location of their division plane in the cell) to produce cells with fates that either differ from (Fig. 1b), or are the same as, that of the original dividing cell (Fig. 1c). Using a custom-made device — a light-sheet confocal microscope — the authors obtained images providing detailed spatial and temporal information regarding SHR–SCR expression during root growth. These high-speed 3D images were acquired with minimal loss of fluorescent signals (a problem known as photobleaching) and enabled the researchers to view protein dynamics in space and time. This would have been tedious to achieve using conventional microscopy methods of confocal imaging.

The authors imaged three proteins, SHR, SCR and the nuclear protein H2B, each tagged with a different fluorescent molecule, and evaluated the dynamics of their expression. Winter

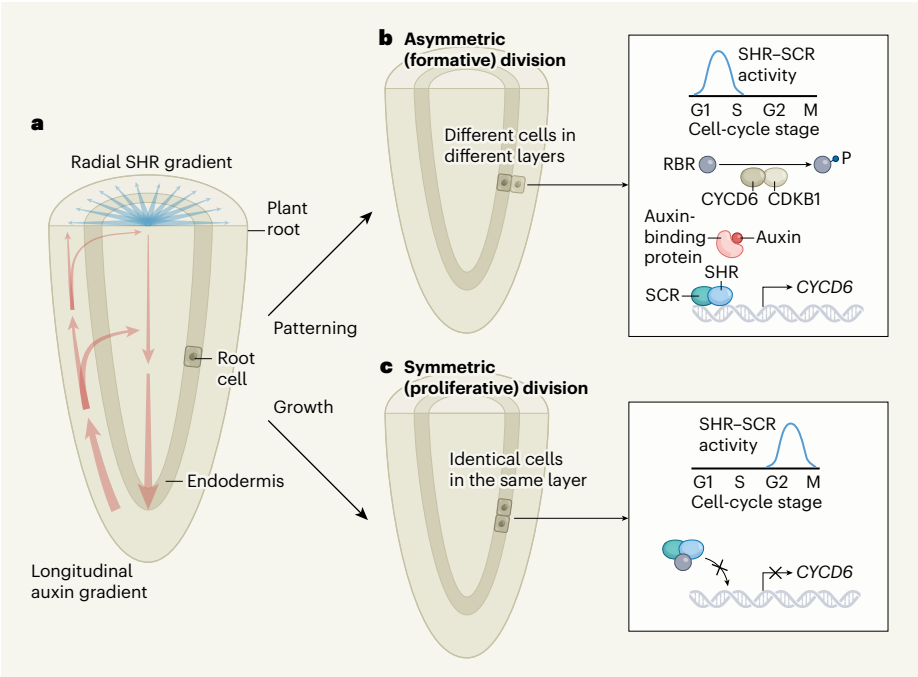

Figure 1 | Control of asymmetric cell division in the root. **a**, In the plant *Arabidopsis thaliana*, gradients of the molecules auxin and SHR aid processes that govern cell division. Auxin is highest at the root tip of its longitudinal gradient[6], and SHR is highest at the root's centre and runs outwards in a radial gradient[5]. For a given cell, such as the one shown in the layer called the endodermis, the orientation of cell division determines whether the cell divides asymmetrically to give rise to two different cell types and two distinct tissue types, or symmetrically to form identical cells in the same layer. **b**, Winter *et al.*[1] present microscopy data that shed light on cell division. In asymmetric (also called formative) division, a complex of the transcription factors SHR and SCR is active during cell-cycle stages called G1 and S. The proteins CDKB1 and CYCD6 phosphorylate (add a phosphate (P) group) to the protein RBR. The gene *CYCD6* is expressed through the action of the SHR–SCR complex and by auxin bound to an auxin-binding protein[3]. **c**, During symmetric (also termed proliferative) division, the SHR–SCR complex is active at the cell-cycle stages G2 and M. RBR does not contain a phosphate group, and it binds to the SHR–SCR complex, thereby preventing *CYCD6* expression.

and colleagues then used this information to determine how often cells divide asymmetrically compared with symmetrically. The authors found that SHR-mediated asymmetric division occurs only during a limited window of the cell cycle.

The authors used mathematical models that revealed that bistability is not a prerequisite for SHR–SCR action. This outcome might seem inconsistent with the findings described previously[3]. However, it can also be considered as an alternative model for bistability – especially given that the authors also observed an increase in the level of SHR, and this level of SHR remained constant until division took place, then the level decreased, which is consistent with previous findings.

The authors found that the absence of SHR from a cell during a specific stage of the cell cycle affects its commitment to divide asymmetrically or symmetrically. They demonstrated this through a mathematical approach and confirmed it experimentally by synchronizing cells at particular stages of the cell cycle, using cell-cycle inhibitors. The induction of SHR expression after the cells were released from inhibition of the transition between the G1 and S stages of the cell cycle triggered a higher frequency of asymmetric cell divisions than was observed after the release from transition between the G2 and M stages of the cell cycle.

In the region of the root called the meristem, cells have the potential to undergo both types of division. Another interesting observation made by the authors was the inability of SHR to initiate asymmetric cell divisions outside the meristem, indicating that other factors, including the auxin gradient necessary for SHR–SCR action, as well as all the components of the signalling network needed for asymmetric division, are probably expressed exclusively in the meristem. Examining these components experimentally will provide more insights into the requirement for SHR in triggering divisions in a differentiated cell.

The authors worked in the laboratory of Philip Benfey, who died in 2023. When those of us who knew him think about Benfey, some of the attributes that come into our mind include vision, leadership, intelligence, generosity, kindness, optimism and courage. The plant developmental biology community has lost an outstanding scientist, a fantastic person, a great mentor and leader. His passion, dedication, innovation in research and his support for the young generation, especially female researchers, have inspired us all. His optimism and courage were contagious and gave us all hope for the future. He will always be in our hearts, and his legacy will live on.

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1. Winter, C. M. *et al. Nature* **626**, 611–616 (2024).
2. Sozzani, R. *et al. Nature* **466**, 128–132 (2010).
3. Cruz-Ramírez, A. *et al. Cell* **150**, 1002–1015 (2012).
4. Di Laurenzio, L. *et al. Cell* **86**, 423–433 (1996).
5. Helariutta, Y. *et al. Cell* **101**, 555–567 (2000).
6. Grieneisen, V. A., Xu, J., Marée, A. F. M., Hogeweg, P. & Scheres, B. *Nature* **449**, 1008–1013 (2007).
7. Yao, G., Lee, T. J., Mori, S., Nevins, J. R. & You, L. *Nature Cell Biol.* **10**, 476–482 (2008).

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Neuroscience

How the brain produces and perceives speech

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A neural probe has been used to capture the activity of large populations of single neurons as people are speaking or listening, providing detailed insights into how the brain encodes specific features of speech. **See p.593 & p.603**

In the human brain, the perception and production of speech requires the tightly coordinated activity of neurons across diverse regions of the cerebral cortex. On pages 593 and 603, respectively, Leonard *et al.*[1] and Khanna *et al.*[2] report their use of a neural probe consisting of an array of microelectrodes, called Neuropixels, to measure the electrical activity of individual neurons in regions of the human cortex involved in speech processing.

Speech has a sophisticated structure that is characterized by the hierarchical organization of sounds across various timescales. Phonemes, the smallest units of speech, underpin spoken language and contribute to the differentiation of words and syllables. For instance, the three-phoneme words 'dig', 'dug', 'dog' and 'god' differ only by the alteration of a single phoneme (/dɪg/ versus /dʌg/ versus /dɒg/) or the rearrangement of phonemes (/dɒg/ versus /gɒd/).

Despite advances in scientists' understanding of the intricate neural computations involved in parsing and recognizing phonemes, it is still not clear how the brain represents the identity and sequence of phonemes at the level of single neurons. Are single neurons tuned to single phonemes (/ɪ/ versus /ʌ/ versus /ɒ/) by showing distinct responses to each? Or, instead, are neurons selective for groups of phonemes, much as neurons in the visual cortex are tuned to classes of object, such as faces[3]? And do neurons encode sequences of phonemes (such as /dɒg/ and /gɒd/)?

To address these questions, intracranial neural recordings can be made in people who are performing speech tasks[4,5]. Researchers in the same groups as Leonard *et al.* and Khanna *et al.* demonstrated in 2022 that it is possible to perform single-neuron recordings in people undergoing brain surgery while awake using Neuropixels electrodes[6,7] – a method that had previously been used only in non-human animals[8]. In their latest studies, the authors have captured the stable, simultaneous activity of tens of single cortical neurons while participants were either listening to speech[1,2] or speaking[2] (Fig. 1). Their groundbreaking work represents the first applications of Neuropixels to address meaningful research questions that can be answered only in humans.

The authors' detailed insight into the single-neuron encoding of speech perception and production yields two key findings. First, they show that single neurons are selectively tuned to groups of phonemes that are articulated in a similar way. This mirrors findings obtained with a more conventional intracranial electrophysiology method, called electrocorticography, in which electrical activity is averaged from hundreds of cells[5]. Second, these studies show how the coordinated activity of neuronal populations encodes emergent properties of speech perception and production.

Leonard and colleagues recorded neural activity from a region of the brain's auditory cortex called the superior temporal gyrus. This cortical region is specialized for high-level processing of speech sounds before the meanings of words are processed in other brain regions. Khanna and colleagues focused on a part of the brain's prefrontal cortex that is involved in word planning and sentence construction.

When participants were listening to speech, single neurons in both the auditory cortex[1] and the prefrontal cortex[2] were tuned to classes of phoneme (defined by their similar articulation) rather than specifically to single phonemes. Neurons that were spatially close to each other tended to show correlated functional