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Centre for Ecology and Conservation, School of Biosciences, University of Exeter, Cornwall TR10 9EZ, UK.
E-mail: D.J.Hosken@exeter.ac.uk

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Cell Division: Mid-Level Management

When a fission yeast cell divides, the anillin-like protein mid1p helps to position the contractile ring in the cell middle. Recent experiments from two groups have shown how the cell-polarity factor pom1p negatively regulates the distribution of mid1p.

Kenneth E. Sawin

Accurate partitioning of genomes during cell division requires not only high-fidelity chromosome segregation but also proper positioning of the actomyosin contractile ring that drives cytokinesis in animal and fungal cells. In animal cells, the position of the ring is determined by both positive and negative signals from the mitotic spindle (summarized in [1]), while in the budding yeast *Saccharomyces cerevisiae*, the ring forms at the site of bud emergence (see [2] for references). In the fission yeast *Schizosaccharomyces pombe*, which is rapidly becoming a popular model for quantitative studies of cytokinesis [3,4], the position of the cell nucleus positively and dynamically signals the future position of the contractile ring [5–7], via the protein mid1p [8,9]. New results [10,11] now indicate that negative signals also act to specify contractile ring position in fission yeast, and that these also operate via mid1p.

Mid1p was first identified from loss-of-function mutations in which the contractile ring is able to form, but its position is uncoupled from the position of the nucleus [8,9]. As a consequence of this, although *mid1* is not an essential gene *per se*, *mid1Δ* cells grow relatively poorly. Initial localization studies showed mid1p to be in the nucleus during interphase and at the plasma membrane during mitosis, first as spots within a broad ring in the cell middle and later as a tight ring, thus displaying some properties similar to the related protein anillin of higher eukaryotes (see [12] for references). Temporally, mid1p is one of the 'earliest' cortical factors known to be involved in contractile ring formation, and recent work has suggested that membrane-associated 'nodes' of mid1p may recruit myosin II and other proteins to the cell cortex, later coalescing to form a ring [3,13,14].

The movement of mid1p from nucleus to plasma membrane is thought to coordinate nuclear position with contractile ring placement. To do this accurately requires a dynamic localization of mid1p, and a key element of this scenario is that mid1p shuttles between nucleus and cytoplasm to become associated with the cortex. This has been borne out in experiments where both nuclear localization signals and nuclear export signals within mid1p have been manipulated [15].

While initial immunofluorescence observations using anti-mid1p antibodies showed a cortical membrane localization for mid1p only in mitosis, visualization of mid1–GFP fusions in living cells later revealed that mid1p is at the cortical membrane during interphase as well, specifically in the middle of cells, and this localization also follows the position of the nucleus [15]. (While GFP-tagged mid1 is functional and provides the basis for nearly all subsequent work, it should be noted that there is some evidence that it does not behave exactly like untagged mid1p [11,15,16].)

This sets the stage for the question: can a simple mechanism of shuttling from the nucleus to the membrane actually account for the interphase mid1p distribution seen *in vivo*, with a strong enrichment in the cell middle? In a collaboration between the Chang and Howard groups, Padte *et al.* [10] addressed this question by constructing an explicit mathematical model for

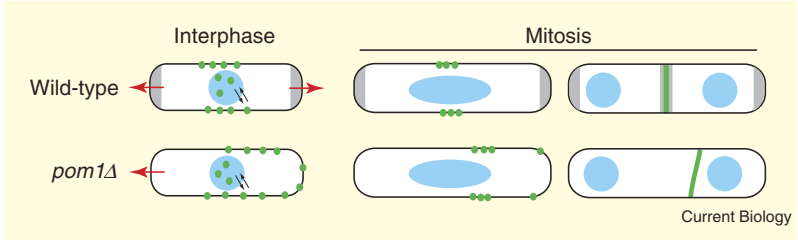

Figure 1. A summary of mid1p distribution in wild-type and *pom1Δ* cells during interphase and early and late mitosis.

Cell nuclei are shown in blue. Mid1p is shown in green. For simplicity, cytoplasmic pools of mid1p are not shown. Pom1p is shown at cell tips in gray; *in vivo*, pom1p displays a gradient of localization towards cell tips, which is not shown here. Red arrows indicate patterns of cell growth, and small black arrows indicate diffusion of mid1p in and out of the nucleus. In interphase *pom1Δ* cells, mid1p is more spread out on the plasma membrane, and biased towards the non-growing end. As a result, in mitotic *pom1Δ* cells, mid1p is not properly centered in the cell.

mid1p localization, based on a series of differential equations with some adjustable parameters. The essentials of the model are relatively simple: intranuclear mid1p can diffuse within, or be exported from, the nucleus; cytoplasmic mid1p can diffuse in the cytoplasm, bind to the plasma membrane, and/or be reimported into the nucleus; and plasma-membrane-bound mid1p can diffuse within the membrane or be released into the cytoplasm. For simplicity, the model was created in one dimension rather than three, but straightforward qualitative arguments suggest that this should not alter the basic results. Surprisingly, the conclusion is that simple diffusion-based mechanisms cannot account for the relatively tight interphase membrane distribution of mid1p. While a solely diffusion-based mechanism can result in some enrichment of mid1p at the cell middle as compared to the rest of the membrane, this is quite feeble relative to what is actually observed [10].

How then to modify the model? Padte *et al.* [10] pursued the idea that gradients of 'polar inhibitors' at cell tips might prevent the association of mid1p with the plasma membrane. When such hypothetical inhibitors were incorporated into the model, a much tighter distribution of mid1p was obtained. To try to determine whether such inhibitors actually exist, and what form(s) they might assume, Padte *et al.* [10] examined mid1–GFP localization in a number of *S. pombe* strains containing mutations in cell-polarity factors that are normally localized to cell tips. Strikingly, they found that in cells deleted for the DYRK-family protein kinase pom1p [17,18], mid1p distribution was altered in a manner suggesting that pom1p was one of the sought-after polar inhibitors (see below).

At this point, the work converges with parallel experiments from Paoletti's group [11], who were independently looking at mid1p localization in *pom1Δ* cells. It was known that, in addition to having a 'monopolar growth' phenotype, in which cells grow at only one end instead of two, *pom1Δ* cells show defects in positioning the contractile ring, including mis-positioning of the mid1p ring (Figure 1) [17]. In this context, Celton-Morizur *et al.* [11] wanted to know whether the effects of *pom1Δ* on mid1p distribution were specific to mitosis or already present during interphase. To improve imaging of interphase mid1p, Celton-Morizur *et al.* [11] tagged mid1p with four copies of GFP, and they also applied automated image analysis to obtain a more quantitative picture of mid1p distribution.

The results obtained by the two groups [10,11] are largely overlapping, with many variations. But overall, the basic finding is that in *pom1Δ* cells, the membrane distribution of mid1p is no longer central and tight, but rather more spread out, and strongly biased towards one cell end — in all cases, the non-growing end of monopolar *pom1Δ* mutants (Figure 1). Further experiments showed, among other things, that pom1p kinase activity is required for proper mid1p distribution, and that, in spite of the lack of "coupling" between nuclear position and mid1p distribution in *pom1Δ* cells, mid1p distribution is still responsive to nuclear positioning in these cells.

From these experiments, two observations in particular stand out. First, although several monopolar growth mutants were analyzed for defects in mid1p positioning, only *pom1Δ* mutants have a very strong defect. This indicates that the role of pom1p in regulating mid1p is unlikely to be an indirect consequence of monopolar growth. This is important because mutations in some polarity factors have previously been shown to confer 'middle-like' properties to cell ends [19]. On the contrary, it seems likely that growth polarity and mid1p regulation are two independent 'downstream targets' of pom1p. While some additional monopolar growth mutants did show some defects in mid1p positioning, these were primarily mutants that alter pom1p localization itself.

Second, from the exclusion of mid1p from the growing end of *pom1Δ* cells, it is clear that there must be a second, pom1p-independent mechanism of polar inhibition at growing cell ends. Preliminary evidence from the Chang group suggests that active growth — in particular, an intact actin cytoskeleton — is involved, but the details remain completely unknown.

What does the future hold? Certainly one would like to know whether pom1p is phosphorylating mid1p directly. Mutation of the three consensus DYRK-family kinase phosphorylation sites [18] in mid1p did not alter its distribution in wild-type cells [11], suggesting that the inhibitory effects of pom1p on mid1p may be indirect. In this case, it will be of great interest to identify the substrates of pom1p, and also to determine how modifications of mid1p near cell tips cause it to leave the plasma membrane, or fail to bind at all.

Mid1p binding to the membrane is complex, as both amino- and carboxy-terminal fragments of mid1p can bind to the membrane independently, and both fragments also show self-interaction in immunoprecipitation experiments [16]. Thus, it seems possible that the oligomerization state of mid1p may be an important factor in regulating its distribution.

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Wellcome Trust Centre for Cell Biology, University of Edinburgh, Swann Building, Mayfield Road, Edinburgh EH9 3JR, UK.
E-mail: ken.sawin@ed.ac.uk

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Cognitive Training: Neural Correlates of Expert Skills

Expertise is a ubiquitous pre-requisite for modern life, but little is known about what neural mechanisms underpin the acquisition or employment of such skills. Recent evidence from functional magnetic imaging studies suggests that a network of frontal and parietal regions plays a crucial role.

Daniel Bor and Adrian M. Owen

Perhaps our most defining feature as a species is the ability to become experts in an array of mental tasks. While the skills of a champion chess player or professional musician are tremendous, many of us still show considerable expertise every day, such as whenever we use a computer or carry out various tasks at our workplace. Although much is known about the psychology of expertise, until recently there was a paucity of knowledge concerning what brain mechanisms give rise to such marked abilities. Three recent brain imaging studies have shed considerable light on this field [1–3]. These new data suggest that a network of regions comprising the lateral prefrontal cortex and posterior parietal cortex drive increased performance on tasks requiring memory skill, are critical for the use of such abilities, and dynamically co-ordinate a set of supporting regions to facilitate expertise.

One of the first studies to investigate the neural correlates of training and expertise was that of Olesen *et al.* [3]. Participants underwent training for five weeks on a battery of visual working memory tasks, and were scanned using functional magnetic resonance imaging (fMRI) before, during and after training. Consistent with previous studies [4], subjects not only improved significantly in their working memory capacity, but also on general cognitive tests that they had never trained on. As participants' working memory performance improved, the lateral prefrontal and posterior superior parietal cortex increased in activation. It was not clear, however, whether these regions were driving enhanced performance, or were simply working memory areas with more processing to carry out now that the subjects had increased in proficiency. Furthermore, the expertise of the participants was weak and of a very general nature, further limiting the conclusions of this research.

In their recent study, Moore *et al.* [2] examined expertise in a more specific way. Over the course of 10 days prior to scanning, participants were trained to become proficient at recognising one class of highly