

IN FOCUS

How mitotic spindles point to the exit

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Study reveals that an interaction between myosin-10 and Wee1 may link spindle positioning to mitotic progression.

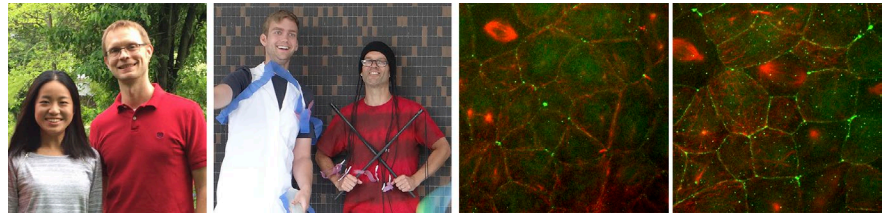
Epithelial cells generally position their mitotic spindle near the center of the cell and orient it parallel to the plane of the epithelium so that, when the cell divides, it generates two equally sized daughter cells that remain within the epithelial layer. It is unclear if, or how, cells delay mitotic progression and cytokinesis until their spindles are in the right place but Sandquist, Larson et al. suggest that an interaction between the motor protein myosin-10 and the cell cycle regulator Wee1 could help coordinate spindle positioning and mitotic exit (1).

In the *Xenopus* embryonic epithelium, metaphase spindles rotate into the correct orientation and then make a series of rapid, oscillatory movements that brings them into contact with the cell cortex, before finally settling in the center of the cell (2). “If spindle orientation is important, there ought to be some sort of mechanism for the cell to decide whether or not the correct orientation has been achieved before it goes any further through mitosis,” says Joshua Sandquist, from Grinnell College in Iowa.

Myosin-10, which binds to both actin and microtubules, could play an important role in such a mechanism, because it appears to regulate both spindle dynamics and mitotic progression (3). Sandquist and his team previously found that a dominant-negative fragment of myosin-10, encompassing the protein’s MyTH4 domain, can delay the metaphase-to-anaphase transition in *Xenopus* epithelial cells (4).

Now, Sandquist and colleagues, including Matthew Larson and Bill Bement from the University of Wisconsin-Madison, found that myosin-10’s MyTH4 domain binds to Wee1 (1). The two proteins colocalized near the poles of *Xenopus* mitotic spindles.

Though Wee1 is best known for its role in preventing mitotic entry, it can also, at least in budding yeast, delay anaphase onset by



Focal Point (Left to right) Zhiwei Ding, Joshua Sandquist, Matthew Larson, Bill Bement, and (not pictured) Sarah Woolner reveal that an interaction between myosin-10 and Wee1 may help epithelial cells delay mitotic exit until their spindle is positioned and oriented correctly. The researchers identify a pool of inactive, Wee1-phosphorylated Cdk1 (green) at tricellular junctions, close to sites where the correctly oriented spindle (whose microtubules are labeled red) makes contact with the cell cortex. In control cells (left), this pool of inactive Cdk1 is depleted during metaphase, allowing cells to exit mitosis. But expression of dominant-negative myosin-10 (right) enhances the pool of inactive Cdk1 and delays anaphase onset. PHOTOS COURTESY OF THE AUTHORS.

phosphorylating and inhibiting cyclin-dependent kinase 1 (Cdk1; 5). Sandquist and colleagues confirmed that Wee1 also delays anaphase onset in *Xenopus* epithelial cells. But where does Cdk1 localize in these cells? As expected, there were pools of cyclin B-Cdk1 in the nucleus and on the mitotic spindle, but the researchers also saw the kinase at the apical cell-cell junctions, particularly at tricellular junctions where three epithelial cells contact each other.

Tricellular junctions are thought to be important landmarks for spindle orientation and are frequently near to the sites where oscillating spindles contact the cell cortex (2, 6). The researchers found that the inactive, Wee1-phosphorylated form of Cdk1 was enriched at tricellular junctions for most of the cell cycle, but showed a slight decrease during metaphase and anaphase. Expression of myosin-10’s MyTH4 domain elevated junctional phospho-Cdk1 levels, however, indicating that this fragment delays mitotic exit by enhancing Wee1 activity and inhibiting Cdk1. Accordingly, treating cells with a Wee1 inhibitor relieved the metaphase delay induced by MyTH4.

Knocking down myosin-10, or inhibiting Wee1, suppressed the normal, oscillatory movements of the metaphase spindle, sug-

gesting that these movements are somehow responsible for initiating mitotic exit. To test this idea, the researchers used an independent method of inhibiting spindle movements, expressing a plasma membrane-targeted version of the dynactin subunit dynamitin to disrupt the function of cortical dynein in spindle positioning, without inhibiting cytoplasmic dynein’s various roles in maintaining spindle structure and function. “And, yes, we saw that the spindles don’t oscillate like normal and the cells don’t progress through mitosis,” Sandquist says.

The researchers think that when the oscillating spindle contacts the cortex near tricellular junctions, it may deliver active cyclin B-Cdk1 and/or remove Wee1. “Either way, you would end up with a local increase in Cdk1 activity at cortical sites that line up with spindle orientation, allowing Cdk1 to initiate mitotic exit,” Sandquist explains. The researchers hope to test this idea by developing improved biosensors to track Cdk1 activity in live cells.

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