CYTOSKELETON

Tracking the weakest link

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> “Mal3 binds to and stabilizes microtubules through a specific interaction…”

Precise control of microtubule dynamics is achieved by several microtubule-associated proteins (MAPs), including the recently discovered plus-end tracking proteins (+TIPs). Sandblad *et al.* now report that the fission yeast +TIP, Mal3, interacts with microtubules in a very different way from other MAPs — Mal3 binds to and stabilizes microtubules through a specific interaction with the microtubule-lattice seam, which is potentially the weakest part of the microtubule.

End binding-1 (EB1) proteins are conserved regulators of eukaryotic microtubule dynamics and exert growth-promoting or stabilizing functions. EB1 has been shown to ‘track’ the plus ends of microtubules, and it has been proposed that this protein might form part of a scaffold that recruits other proteins to the growing plus ends. Like EB1, its human homologue, fission yeast Mal3 accumulates at growing microtubule plus ends, but it also localizes along the microtubules. However, partly due to the limited resolution of light microscopy, the interactions and functions of this protein remained hidden.

To overcome these constraints and to investigate the interactions of Mal3 with the microtubule using a molecular-level approach, Sandblad *et al.* studied the interactions of Mal3 with microtubules by electron microscopy (EM) and high-resolution metal shadowing. Surprisingly, they found that Mal3 binds to the weak point of the microtubule, the so-called seam — a discontinuity in the microtubule wall that is due to the helical nature of a tube formed with a heterodimeric complex (consisting of α- and β-tubulin). This structural peculiarity can be seen as a structural necessity for closing the tube properly. EM analysis showed that Mal3 molecules align within the groove of the seam. To confirm these results, the authors carried out biochemical experiments, which showed that Mal3 stabilizes microtubules by promoting the closed-tube versus the open-sheet conformation. Therefore, cells seem to use EB1 proteins to reinforce the microtubule seam.

Is the function of Mal3 conserved, and do the mammalian EB1 proteins also bind to the microtubule lattice? Are the properties of Mal3 plus-end binding different from those of microtubule-lattice binding? And how does EB1 (or Mal3) track the plus ends of microtubules, given that EB1 proteins in cells mainly bind to the plus ends of growing microtubules? Although technically challenging, addressing these questions will shed further light on the mysteries of plus-end tracking.

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FURTHER READING Kikkawa, M. & Metlagel, Z. A molecular “zipper” for microtubules. *Cell* **127**, 1302–1304 (2006)

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