

## Cytoskeleton key

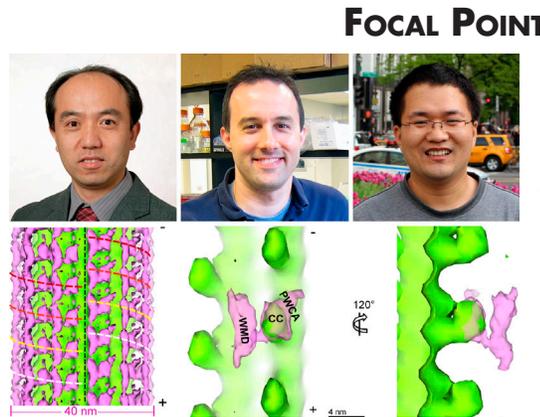
Study uncovers mechanism for integrating microtubules and actin.

The protein WHAMM serves as an intermediary between the microtubule and actin cytoskeletons. Shen et al. discover that binding to microtubules changes WHAMM's interactions with actin, offering insight into how cells keep the two cytoskeletons in sync (1).

Researchers have mainly studied the microtubule and actin cytoskeletons separately. For example, they've uncovered how actin dynamics shape the cell and enable it to crawl and divide (2). And scientists have detailed microtubules' roles during mitosis and vesicle transport (3, 4). But knowledge of how cells integrate changes to the two cytoskeletons during activities such as these remains sketchy. A possible link between the two cytoskeletons is WHAMM, an actin filament–nucleating protein that also binds microtubules (5). WHAMM sports a coiled-coil region in its midsection that connects to microtubules, an N terminus that fastens onto lipids, and a C terminus that hooks onto actin monomers and the Arp2/3 complex, which spurs actin polymerization and branching. The protein dwells at the Golgi apparatus and on membrane vesicles that travel from the ER to the Golgi. One of WHAMM's jobs is to help stretch the spherical vesicles that bud from the ER into a tubular shape. Their elongation, which might enable them to carry particularly large molecules, requires actin filaments and microtubules (5).

Shen et al. took a close look at WHAMM's interactions with microtubules using cryoelectron microscopy. The team's 3D reconstructions of WHAMM molecules bound to microtubules showed that U-shaped WHAMM molecules line up head to tail along the microtubule protofilaments. WHAMM's coiled-coil region clamps to the microtubule, whereas the N terminus juts out. The C terminus, on the other hand, is tucked beneath the rest of the molecule.

**“When WHAMM binds to microtubules, it seems to be fairly inactive for stimulating actin nucleation.”**



(Top, left to right) Hong-Wei Wang, Kenneth Campellone, Qing-Tao Shen, and colleagues (not pictured) delineated how the protein WHAMM coordinates the actin and microtubule cytoskeletons. WHAMM molecules (purple in lower images) attach to microtubules (green) in a head-to-tail formation. A close-up of a WHAMM protein (lower, center and right) shows that the membrane-binding N terminus (WMD) juts out from the microtubule-interacting coiled-coil segment (CC) and overhangs the actin-nucleating C terminus (PWCA).

PHOTOS COURTESY OF JERRY DOMAN (WANG), CHRISTINE BUCKLEY (CAMPELLONE), AND YUNHUI LIU (SHEN)

That architecture suggests how WHAMM works, because the protruding N terminus is in position to latch onto vesicles that need to be stretched. To test that possibility, the researchers gave WHAMM proteins the opportunity to grab liposomes in vitro. The lipid spheres attached to WHAMM proteins affixed to microtubules but not to coiled-coil segments bound to microtubules or to WHAMM-free filaments. Cryo-EM revealed that the captured liposomes lengthened.

Buried beneath the molecule, WHAMM's C terminus is in a poor position to nucleate actin. The researchers gauged this ability by measuring how fast actin assembled in the presence of Arp2/3 and different variants of WHAMM. Full-length WHAMM or only its C terminus caused swift actin polymerization, much faster than Arp2/3 alone. But fiber growth was sluggish when the team mixed full-length WHAMM with microtubules. “When WHAMM binds to microtubules, it seems to be fairly inactive for stimulating actin nucleation,” says co-author Kenneth Campellone.

The study reveals one way that the microtubule cytoskeleton, acting through WHAMM, influences the actin cytoskeleton, although how the cell benefits from

thwarting actin nucleation during vesicle elongation isn't clear. Reduced nucleation might hinder the formation of branched fibers that could prevent the vesicle membrane from extending along a microtubule, but previous work has demonstrated that actin filaments are indeed necessary for vesicles to stretch. The researchers speculate that WHAMM molecules that haven't attached to microtubules could trigger actin nucleation or branching, spawning filaments that reshape the vesicles. Researchers still need to work out which cargo molecules are packaged into these membrane tubules and what other proteins interact with WHAMM during tubule formation. But WHAMM has shown itself to be a versatile protein that could make an even bigger impact in the cell. “The fact that it can interact with three fundamental parts of the cell suggests that it could be at the heart of a lot of important processes,” says Campellone.

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