Regulation of g-tubulin Ring Complex-mediated Microtubule Nucleation by Micro-proteins, Mzt1 and GCP8

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Abstract

Microtubules self-assemble *in vitro* from purified α/β tubulin heterodimer at a higher tubulin concentration compared to at cellular levels (~5 μM in *Schizosaccharomyces pombe*). Therefore, *de novo* microtubule assembly is kinetically limited in cells. To overcome this kinetic barrier, *in vivo* microtubule nucleation in higher eukaryotes is promoted primarily by the γ-tubulin ring complex (γ-TuRC), an evolutionarily-conserved protein complex with a molecular weight of more than 2 MDa that comprises γ-tubulin (a member of the tubulin family) together with multiple proteins including two microproteins Mozart1 (Mzt1) and GCP8.

γ-TuRC has been proposed to function as a master template for microtubule nucleation. However, how two microproteins interact with γ-TuRC and modulate its functions remains nuclear. Here, we report that Mzt1 and GCP8 facilitate γ-TuRC-mediated microtubule formation and cilia disassembly respectively. Crystal structures of protein complexes demonstrate that Mzt1 and GCP8 interact with the N-terminal domains of multiple γ-tubulin complex protein subunits in γ-TuRC via an intercalative binding mode[1,3]. Furthermore, while Mzt1 and GCP8 complexes share the same binding mode, different localizations of the complexes in γ-TuRC revealed by cryo-EM study suggest that they can modulate γ-TuRC assembly and mediate interactions with other proteins[2]. Next, genetic and microscopy-based analyses show that promiscuous binding of Mzt1 in γ–TuRC controls specific subcellular localization of γ-TuRC to modulate microtubule nucleation and stabilization in fission yeast[1]. Moreover, we found Mzt1-independent targeting of γ-TuRC to be crucial for mitotic spindle assembly, demonstrating cell cycle-dependent regulation and function of γ-TuRC[1]. In addition to controlling microtubule formation facilitated by Mzt1, we further find that γ-TuRC recruits a kinesin motor, Kif2A, through GCP8 and thereby promotes cilia disassembly in mammals[3]. Hence, our findings reveal a microprotein-mediated regulatory mechanism underlying microtubule assembly and microtubule-based organelle formation.

Keywords – microtubule nucleation, γ-tubulin ring complex, cytoskeleton, cilium

References

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