Temporal Dissection of Microtubule-based Motor CENP-E in Mitosis

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Chromosome movements during mitosis are orchestrated primarily by the interaction of spindle microtubules with the kinetochore, the site for attachment of spindle microtubules to the centromere. The kinetochore has an active function in chromosomal segregation through microtubule-based motors located at it. Mitotic motor CENP-E plays key roles in chromosome congression and spindle checkpoint satisfaction. Our lab has identified and characterized syntelin, a novel selective CENP-E inhibitor (Ding et al., 2010. Cell Res.). Cells treated with syntelin progress through interphase, enter mitosis normally with a bipolar spindle and lagging chromosomes around the poles. Syntelin is an allosteric inhibitor which tightens CENP-E-microtubule interaction by slowing inorganic phosphate release. To delineate the temporal involvement of CENP-E in reorganization of interpolar microtubules into an organized central spindle during metaphase-anaphase transition in mitosis, metaphase synchronized cells were exposed to syntelin and other mitotic motor inhibitors. Syntelin does not perturb interpolar microtubule assembly but abrogates the anti-parallel microtubule bundle formation. Real-time image shows that CENP-E inhibited cells undergo central spindle splitting and exhibits chromosome instability phenotypes. Inhibition of CENP-E did not alter the interaction between CENP-E and microtubule bundling protein PRC1 but perturbed temporal assembly of PRC1 to the midzone. Yet, inhibition of CENP-E perturbs the temporal control of PRC1 dephosphorylation which led to a persistent phosphorylation of PRC1 and an inhibition of central spindle assembly. These findings reveal a previously uncharacterized role of CENP-E motor in temporal control of central spindle assembly during cell division cycle.

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