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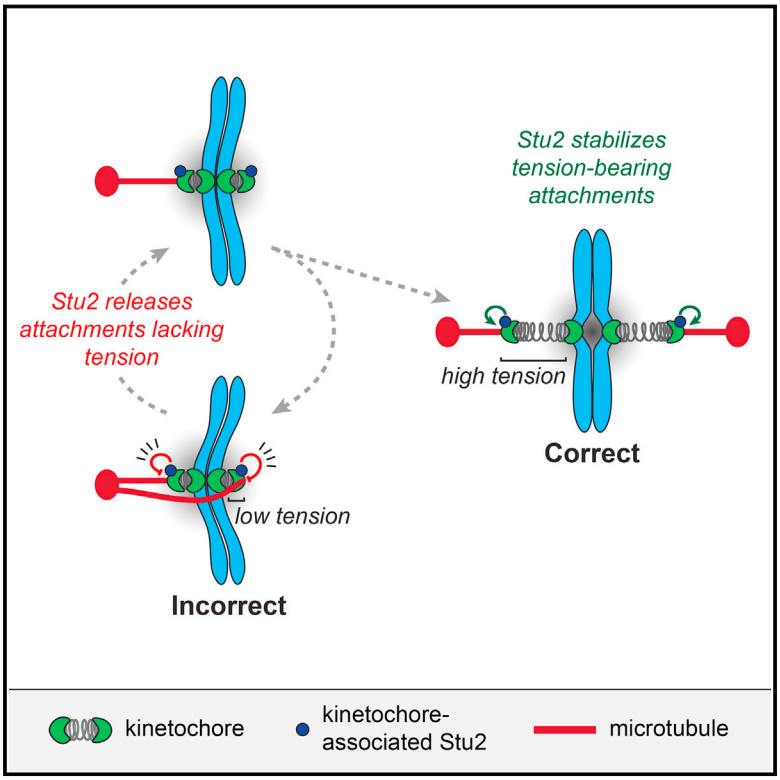
A TOG Protein Confers Tension Sensitivity to Kinetochore-Microtubule Attachments

Graphical Abstract



Highlights

- ch-TOG and Stu2 exhibit a conserved interaction with the Ndc80 kinetochore complex
- Kinetochore-bound Stu2 directly contributes to microtubule attachment stability
- Stu2's kinetochore function is force and microtubule growth state dependent
- Stu2 selectively stabilizes tension-bearing kinetochore attachments

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In Brief

A protein involved in attachment of spindle microtubules to the kinetochore during chromosome segregation selectively stabilizes tension-bearing attachments because its functional output is context dependent: it can either stabilize or destabilize attachments depending on the level of kinetochore tension and the state of the microtubule tip.

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A TOG Protein Confers Tension Sensitivity to Kinetochore-Microtubule Attachments

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SUMMARY

The development and survival of all organisms depends on equal partitioning of their genomes during cell division. Accurate chromosome segregation requires selective stabilization of kinetochore-microtubule attachments that come under tension due to opposing pulling forces exerted on sister kinetochores by dynamic microtubule tips. Here, we show that the XMAP215 family member, Stu2, makes a major contribution to kinetochore-microtubule coupling. Stu2 and its human ortholog, ch-TOG, exhibit a conserved interaction with the Ndc80 kinetochore complex that strengthens its attachment to microtubule tips. Strikingly, Stu2 can either stabilize or destabilize kinetochore attachments, depending on the level of kinetochore tension and whether the microtubule tip is assembling or disassembling. These dichotomous effects of Stu2 are independent of its previously studied regulation of microtubule dynamics. Altogether, our results demonstrate how a kinetochore-associated factor can confer opposing, tension-dependent effects to selectively stabilize tension-bearing attachments, providing mechanistic insight into the basis for accuracy during chromosome segregation.

INTRODUCTION

Cellular and organismal fitness requires proper partitioning of genetic material during cell division. Failure to accurately segregate chromosomes causes aneuploidy, the most prevalent genetic alteration in tumor cells and a potential factor in the evolution of cancer (reviewed in Gordon et al., 2012). Chromosome segregation is driven by microtubule-based forces, which are generated at kinetochores. The kinetochores must stay bound to microtubule "plus ends," where tubulin subunits are added and lost at a high rate and where the microtubule filaments switch stochastically between phases of assembly and disassembly (Mitchison and Kirschner, 1984).

Kinetochores are conserved macromolecular complexes containing multiple copies of various subcomplexes that assemble onto centromeric DNA (reviewed in Cheeseman, 2014). The major microtubule binding activity within the kinetochore is attributed to the conserved Ndc80 complex (the Ndc80 protein is termed Hec1 in humans) because knockdowns in vivo cause severe defects in kinetochore-microtubule attachment (Cheeseman et al., 2006; DeLuca et al., 2005; McCleland et al., 2004; Wigge and Kilmartin, 2001). However, additional complexes interact with the Ndc80 complex and contribute to attachments, such as the yeast Dam1 complex and its putative functional ortholog, the human Ska complex (Cheeseman et al., 2001; Hanisch et al., 2006; Welburn et al., 2009). While much is understood about how these subcomplexes function alone, it is not known how the activities of these various complexes are coordinated within the larger kinetochore structure. In addition, the extent to which additional kinetochore components contribute to kinetochore-microtubule attachment remains unclear.

To ensure accurate chromosome segregation, sister kinetochores must "biorient," attaching to microtubules from opposite poles, prior to anaphase. Once kinetochores biorient, they come under tension from opposing microtubule pulling forces. Pioneering work showed that incorrect kinetochore attachments are unstable due to the absence of tension (Dietz, 1958; Nicklas and Koch, 1969). The selective release of attachments lacking tension gives the cell another chance to establish proper attachments. While this error correction process relies partly on the Aurora B kinase, which phosphorylates Ndc80 and other kinetochore proteins (reviewed in Carmena et al., 2012; Krenn and Musacchio, 2015), kinetochore-microtubule attachments also possess an intrinsic tension selectivity. Tension directly stabilizes attachments independently of the Aurora B error correction system (Akiyoshi et al., 2010) via two inter-related properties. First, kinetochores bind more stably to assembling tips than to disassembling tips. Second, tension promotes microtubule assembly, which therefore reinforces kinetochore-microtubule attachments at higher forces. Although these properties are sufficient to explain the stabilization of kinetochore-microtubule attachments by tension, specific factors that mediate this activity have not yet been identified.

One conserved family of proteins that localizes to kinetochores and microtubule tips and could therefore contribute to the tension-dependent stabilization of attachments is the XMAP215 family (ch-TOG in humans and Stu2 in budding yeast) (Gard and Kirschner, 1987; He et al., 2001; Hsu and Toda, 2011; Kalantzaki et al., 2015; Ohkura et al., 1988; Tanaka et al., 2005; Tang et al., 2013; Wang and Huffaker, 1997). These proteins generally function as microtubule polymerases by accelerating growth and inhibiting catastrophe (Al-Bassam et al., 2006,