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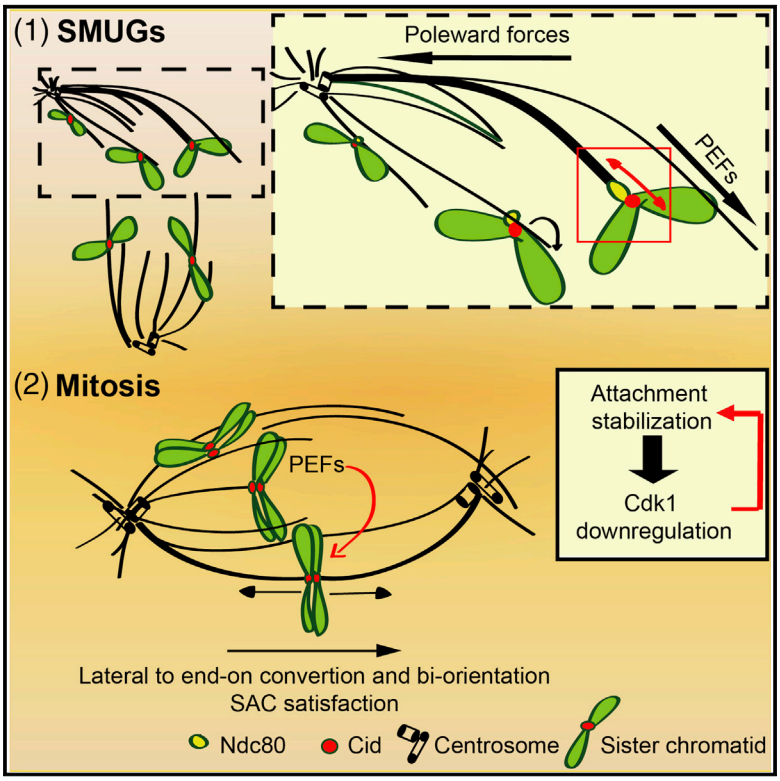
Report

Polar Ejection Forces Promote the Conversion from Lateral to End-on Kinetochore-Microtubule Attachments on Mono-oriented Chromosomes

Graphical Abstract



Highlights

- Spindle assembly checkpoint (SAC) can be satisfied after a delay in cells with mono-oriented chromosomes
- Mono-oriented chromosomes experience intra-kinetochore stretch
- Polar ejection forces promote SAC satisfaction independently of bi-orientation
- Polar ejection forces promote the conversion from lateral to end-on attachments

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In Brief

Tension on bi-oriented chromosomes plays a role in the stabilization of kinetochore-microtubule attachments. However, how kinetochore-microtubule attachments on mono-oriented chromosomes are first stabilized in the absence of tension remained unknown. Drpic et al. now show that polar ejection forces promote the transition from lateral to end-on attachments on mono-oriented chromosomes.

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Polar Ejection Forces Promote the Conversion from Lateral to End-on Kinetochore-Microtubule Attachments on Mono-oriented Chromosomes

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SUMMARY

Chromosome bi-orientation occurs after conversion of initial lateral attachments between kinetochores and spindle microtubules into stable end-on attachments near the cell equator. After bi-orientation, chromosomes experience tension from spindle forces, which plays a key role in the stabilization of correct kinetochore-microtubule attachments. However, how end-on kinetochore-microtubule attachments are first stabilized in the absence of tension remains a key unanswered question. To address this, we generated *Drosophila* S2 cells undergoing mitosis with unreplicated genomes (SMUGs). SMUGs retained single condensed chromatids that attached laterally to spindle microtubules. Over time, laterally attached kinetochores converted into end-on attachments and experienced intra-kinetochore stretch/structural deformation, and SMUGs eventually exited a delayed mitosis with mono-oriented chromosomes after satisfying the spindle-assembly checkpoint (SAC). Polar ejection forces (PEFs) generated by Chromokinesins promoted the conversion from lateral to end-on kinetochore-microtubule attachments that satisfied the SAC in SMUGs. Thus, PEFs convert lateral to stable end-on kinetochore-microtubule attachments, independently of chromosome bi-orientation.

INTRODUCTION

During spindle assembly, the initial lateral interactions between chromosomes and microtubules are converted into stable end-on kinetochore-microtubule attachments that lead to chromosome bi-orientation (Magidson et al., 2011). After chromosome bi-orientation, the opposing spindle forces generate tension on centromeres that is important for the stabilization of correct kinetochore–microtubule attachments required for error-free chromosome segregation (Nicklas and Koch, 1969; Nicklas and Ward, 1994). Tension has also been shown to be sufficient to satisfy the spindle-assembly checkpoint (SAC) (Li and Nicklas, 1995), a surveillance mechanism that ensures that all chromosomes are attached to spindle microtubules before anaphase onset (Foley and Kapoor, 2013). Tension from spindle forces affects kinetochore chemistry through changes in phosphorylation of "tension-sensitive" proteins at kinetochores (Gorbsky and Ricketts, 1993; Nicklas et al., 1995). Aurora B, a mitotic kinase present on centromeres, plays a critical role in tension sensing and error correction (Biggins and Murray, 2001; Cheeseman et al., 2002; Lampson et al., 2004) by phosphorylating key substrates at the kinetochore-microtubule interface, such as the KMN network, in response to tension on bi-oriented chromosomes (DeLuca et al., 2006; Liu et al., 2009; Wang et al., 2011; Welburn et al., 2010). Importantly, recent works in human and *Drosophila* cells have shown that even in the absence of centromeric tension, an intra-kinetochore stretch or structural deformation is sufficient to satisfy the SAC (Maresca and Salmon, 2009; Uchida et al., 2009). However, the underlying mechanism remained unclear.

Chromokinesins are microtubule plus-end-directed motor proteins present on the chromosome arms harboring both chromatin- and microtubule-binding domains. As a consequence of their motor activities, chromokinesins move chromosomes away from the poles by generating random polar ejection forces (PEFs) (Barisic et al., 2014; Brouhard and Hunt, 2005; Levesque and Compton, 2001; Rieder et al., 1986; Wandke et al., 2012; Yajima et al., 2003). Recently, elevated PEFs were shown to stabilize erroneous kinetochore-microtubule attachments (Cane et al., 2013), suggesting a role in the stabilization of kinetochore-microtubule attachments. Here, we found that Chromokinesin-mediated PEFs promote the conversion from lateral to